

*Copy*  
July, 1960

Volume 80, number 1



**COPY 3**  
*American  
Journal  
of* **OBSTETRICS  
AND GYNECOLOGY**

*Editor in Chief*

HOWARD C. TAYLOR, JR.

*Editors*

JOHN I. BREWER · ALLAN C. BARNES

*Official Publication*

AMERICAN GYNECOLOGICAL SOCIETY

AMERICAN ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS

CENTRAL ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS

SOCIETY OF OBSTETRICIANS AND GYNAECOLOGISTS OF CANADA

SOUTH ATLANTIC ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS

*The Journal is also the Official Publication  
of the Societies listed on page 8.*



*Published by*

THE C. V. MOSBY COMPANY  
St. Louis 3, Mo.



## to free patients from anxiety and tension in menstruation • in menopause

**the successor to the tranquilizers.** New Librium can be of invaluable aid to the physician faced by manifold organic manifestations of anxiety and tension. Specifically, the compound has afforded "complete relief" in some cases of intractable dysmenorrhea which previously required narcotics or bed rest.<sup>1</sup> It may prove beneficial in the management of frigidity and infertility;<sup>1</sup> in reducing tensions associated with pregnancy<sup>1</sup> and fears of the menopause.<sup>2</sup> Chemically unrelated to MAO inhibitors, phenothiazines, meprobamate, or any other tranquilizer or antidepressant, Librium is distinguished by unusual safety, specificity and promptness of action. Already evaluated by more than 2,000 physicians in over 20,000 patients, Librium is the subject of 17 published reports.

**Packaging:** Capsules, 10 mg, green and black; 5 mg, green and yellow—bottles of 50 and 500.

**References:** 1. Reports on file, Department of Clinical Investigation, Roche Laboratories. 2. H. A. Bowes, *Dis. Nerv. System*, 21:(Suppl.), 20, 1960.

LIBRIUM<sup>TM</sup> Hydrochloride—7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide hydrochloride

# NEW LIBRIUM

ROCHE  
LABORATORIES



Division of Hoffmann-La Roche Inc.



July  
1960

# Transactions of the Fifteenth Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada

Postmaturity	1
<i>I. A. Perlin, M.D., C.M., F.A.C.S., F.I.C.S., F.A.C.O.G., Halifax, Nova Scotia</i>	
Internal hemorrhage following gynecological operations	6
<i>Robert H. Wesley, M.D., F.R.C.S.(C.), Toronto, Ontario</i>	
Placenta previa	10
<i>William R. Foote, M.D., F.R.C.S.(C.), and William Dennis Fraser, M.D., F.R.C.S.(C.), Montreal, Quebec</i>	
A clinical analysis of abruptio placentae	17
<i>Myer Hendelman, M.D., F.R.C.S.(C.), and William Dennis Fraser, M.D., F.R.C.S.(C.), Montreal, Quebec</i>	
Pelvic tuberculosis	21
<i>D. Nelson Henderson, M.D., John L. Harkins, M.D., and John F. Stitt, M.D., Toronto, Ontario</i>	
Culdoscopy	25
<i>Albert B. Brown, M.D., and Keith M. Crocker, M.D., Saskatoon, Saskatchewan</i>	
Further observations on a simple procedure to eliminate thrush from hospital nurseries	30
<i>L. J. Harris, M.D., M.A., F.R.C.S.(C.), Toronto, Ontario</i>	
The value and danger of exogenous oxytocin in obstetrics	32
<i>C. Lee Buxton, M.D., and Richard Hausknecht, M.D., New Haven, Connecticut</i>	
Pregnancy in the woman over forty	38
<i>Albert L. Higdon, M.D., Teaneck, New Jersey</i>	

(Contents continued on page 2)

## Gynecology

<i>Pelvic exenteration</i>	Details of pelvic exenteration evolved during an experience with 75 cases <i>Robert L. Schmitz, M.D., Herbert E. Schmitz, M.D., Charles J. Smith, M.D., and John J. Molitor, M.D., Chicago, Illinois</i>	43
<i>Cervical biopsy</i>	The cervical cone biopsy-hysterectomy sequence and factors affecting the febrile morbidity <i>Denis Cavanagh, M.D., and Felix Rutledge, M.D., Houston, Texas</i>	53
	Surgical investigation of the cervix with the trachelotome <i>Frank C. Spencer, M.D., and Ralph C. Benson, M.D., Honolulu, Hawaii</i>	60
<i>Carcinoma of the Fallopian tube</i>	Primary carcinoma of the Fallopian tube <i>Paul D. Mozley, Lieutenant (MC) USN, and William S. Baker, Jr., Captain (MC) USN, San Diego, California</i>	64
	Primary carcinoma of the uterine tube <i>J. W. Roddick, Jr., M.D., and D. N. Danforth, M.D., Evanston, Illinois</i>	67
<i>Congenital defects</i>	The syndrome of dysmenorrhea and unilateral gynatresia in a double uterus <i>Guenther C. Merckel, M.D., Moses C. Sucoff, M.D., and Blanka Sender, M.D., Paterson, New Jersey</i>	70
	Male intersex with ambiguous external genitals and well-developed Müllerian elements <i>J. T. Bradbury, Sc.D., and R. G. Bunge, M.D., Iowa City, Iowa</i>	76
<i>Vaginitis</i>	Studies on vaginal flora. I. Frequency and significance of <i>Escherichia coli</i> isolated from vagina <i>Adolfo Pérez-Miravete, Q.B.P., and Hector Jaramillo, Q.B.P., Mexico City, Mexico</i>	80
	A new pediatric gynecologic examining instrument for use in diagnosis of pediatric vaginitis <i>Daniel O. Hammond, M.D., Miami, Florida</i>	85

(Contents continued on page 4)

Vol. 80, No. 1, July, 1960. American Journal of Obstetrics and Gynecology is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. Subscription rates: United States and its Possessions \$15.00; Canada, Latin America, and Spain \$16.00; Other Countries \$17.50. Special rate for medical students and physicians on internship or residency programs, one-half of the domestic rate; for students in other countries, one-half of the domestic rate plus the full amount of the applicable charge for international postage. Single copies \$2.50 postpaid. Second-class postage paid at St. Louis, Mo. Printed in the U. S. A. Copyright © 1960 by The C. V. Mosby Company.

*when anxiety  
accompanies  
somatic complaints*



# STELAZINE<sup>®</sup>

brand of trifluoperazine

*the outstanding tranquilizer that relieves  
anxiety and restores normal drive*

When 'Stelazine' was given, along with appropriate specific medication, "marked relief of emotional and physical symptoms was obtained in 82% of the [120] patients studied.

"Outstanding results were obtained in the patients with gastrointestinal symptoms. . . . In depressed patients, there was a notable restoration of energy and drive, without euphoria."

Phillips, F.J., and Shoemaker, D.M.: Treatment of Psychosomatic Disorders in General Practice, Report accompanying Scientific Exhibit at the 12th Clinical Meeting of the American Medical Association, Minneapolis, Minnesota, Dec. 2-5, 1958.

AVAILABLE—For use in everyday practice: 1 mg. tablets, in bottles of 50 and 500; and 2 mg. tablets, in bottles of 50. STARTING DOSAGE—One 1 mg. tablet, b.i.d. (morning and night). Additional information on request from Smith Kline & French Laboratories, Philadelphia 1, Pa.

SMITH  
KLINE &  
FRENCH

leaders in psychopharmaceutical research

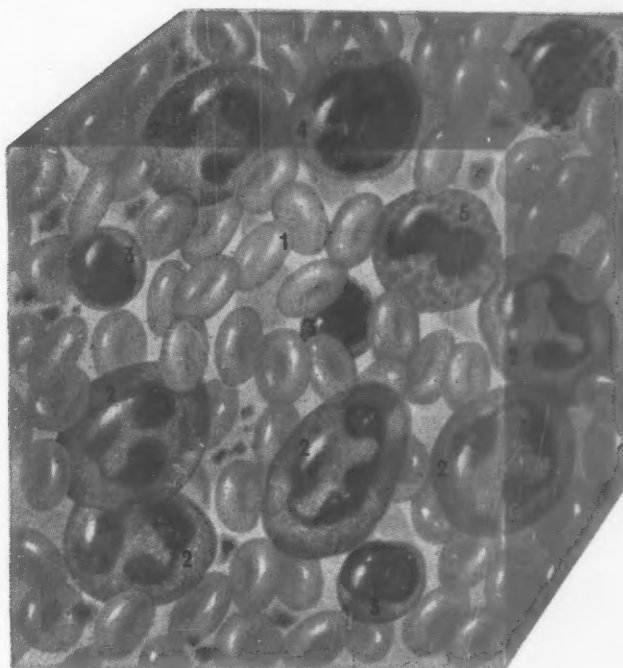
# Contents continued from page 2

## Obstetrics

<b>Physiology of pregnancy</b>	<b>Na<sup>24</sup> uterine muscle clearance in late pregnancy</b>	92
	<i>Robert Landesman, M.D., and Robert Charles Knapp, M.D., New York, New York</i>	
	<b>Glutamic oxalacetic transaminase and lactic dehydrogenase in pregnancy</b>	104
	<i>Martin L. Stone, M.D., Miriam Lending, M.D., Lawrence B. Slobody, M.D., and Joan Mestern, New York, New York</i>	
	<b>Creatinine transport between baby and mother at term</b>	108
	<i>Harry S. McGaughey, Jr., M.D., E. L. Corey, Ph.D., William A. Scoggin, M.D., Conway H. Ficklen, M.D., and W. Norman Thornton, Jr., M.D., Charlottesville, Virginia</i>	
	<b>Serum lipids and protein-bound iodine levels of Guatemalan pregnant women from two different socioeconomic groups</b>	114
	<i>José Méndez, Ph.D., Nevin S. Scrimshaw, Ph.D., M.D., M.P.H., Marvin D. Abrams, and Edwin N. Forman, Guatemala City, Guatemala</i>	
<b>Lactation</b>	<b>Direct measurement of milk ejection pressure in unanesthetized lactating humans</b>	119
	<i>Emanuel A. Friedman, M.D., New York, New York</i>	
	<b>Lactation with a phenothiazine derivative (Temaril)</b>	124
	<i>Harry W. Johnson, M.D., Dasni Poshychinda, M.D., Glenn McCormick, M.D., and E. C. Hamblen, M.D., Durham, North Carolina</i>	
<b>Suppression of lactation</b>	<b>A comparative controlled study of hormones used in the prevention of postpartum breast engorgement and lactation</b>	128
	<i>Karl E. Markin, M.D., and Mack D. Wolst, Jr., M.D., Rochester, New York</i>	
	<b>Suppression of lactation with fluoxymesterone</b>	138
	<i>Wesley W. Bare, M.D., and Frank L. Lippo, M.D., Philadelphia, Pennsylvania</i>	
<b>Medical complications of pregnancy</b>	<b>Effects of mercury on human gestation</b>	145
	<i>Jose F. Afonso, M.D., and Russell R. de Alvarez, M.D., Seattle, Washington</i>	
	<b>Spontaneous rupture of the liver during pregnancy</b>	155
	<i>Allan B. Weingold, Captain, MC, USA, and James W. Thompson, Major, MC, USA, New York, New York</i>	

(Contents continued on page 6)





The standard by which the effectiveness  
of other iron therapy **MUST** be measured

# MOL-IRON®

a specially processed, co-precipitated  
complex of *molybdenized* iron offering  
all these important advantages:

● MORE hemoglobin with ● LESS medication  
in a ● SHORTER period of time ● GREATER  
patient tolerance. ● and . . . costs no more than  
ordinary iron preparations.

There is a MOL-IRON product for all of your  
patient needs, as listed on pp. 878 to 880 in your  
1960 Physicians Desk Reference.



1 Erythrocytes 2 Polymorphonuclear Neutrophile  
3 Lymphocyte 4 Monocyte 5 Eosinophile 6 Basophile  
White Laboratories, Inc., Kenilworth, New Jersey

## Contents continued from page 4

---

	Purpura fulminans complicating pregnancy	161
	<i>R. H. Seinfeld, M.D., G. Hennigar, M.D., and L. M. Hellman, M.D., Brooklyn, New York</i>	
Surgical complications of pregnancy	Pregnancy and delivery following extensive vulvectomy	167
	<i>Jason H. Collins, M.D., Herbert W. Birch, M.D., Max Paillet, M.D., and James K. Avent, M.D., New Orleans, Louisiana</i>	
	Intestinal obstruction associated with pouches and fenestrae in the broad ligament	172
	<i>Harry N. Papas, M.D., Akron, Ohio</i>	
Chorioadenoma and hydatid mole	Chorioadenoma destruens	176
	<i>H. Acosta-Sison, M.D., F.P.C.S., Manila, Philippines</i>	
	Prerenal azotemia and hydatidiform mole	180
	<i>Harold Schulman, M.D., Miami, Florida</i>	

## Department of current opinion

---

Pertinent comments	A note on race-specific congenital malformation rates	184
	<i>Todd M. Frazier, Sc.M., Baltimore, Maryland</i>	
	A rapid method for the office diagnosis of candidiasis	186
	<i>Jed E. Goldberg, M.D., Tulsa, Oklahoma</i>	
	Threatened abortion	187
	<i>Samuel D. Soule, M.D., St. Louis, Missouri</i>	

## Reviews and abstracts

---

Reviews of new books	190
Books received for review	193
Selected abstracts	193

## Correspondence

---

Correspondence	200
----------------	-----

## Roster

---

Roster of American obstetrical and gynecological societies	204
--	-----

**IMPROVING ON NATURE** Plywood is just one of the many examples of how man has modified one of nature's gifts to make it more useful.

In the treatment of hypothyroidism, Proloid offers similar evidence of man's ingenuity in improving on nature.

Proloid is doubly standardized: chemically, like ordinary thyroid, and biologically, by an exclusive Warner-Chilcott assay. This assay assures unvarying metabolic potency and a safe, predictable clinical response in every case. Yet this important extra care makes Proloid cost little more than ordinary thyroid.

Specify Proloid whenever thyroid is indicated. Three grains is the average daily dose for patients with mild forms of hypothyroidism.

*safe, dependable, economical*

**PROLOID®**



MORRIS PLAINS, N.J.

UNITED STATES PLYWOOD CORPORATION

SP03



# American Journal of Obstetrics and Gynecology

---

*in addition to those listed on the front cover,*

*the Journal is the official publication*

*of the following societies:*

NEW YORK OBSTETRICAL SOCIETY

OBSTETRICAL SOCIETY OF PHILADELPHIA

BROOKLYN GYNECOLOGICAL SOCIETY

ST. LOUIS GYNECOLOGICAL SOCIETY

NEW ORLEANS GYNECOLOGICAL AND OBSTETRICAL SOCIETY

THE OBSTETRICAL AND GYNECOLOGICAL SOCIETY OF MARYLAND

CHICAGO GYNECOLOGICAL SOCIETY

CINCINNATI OBSTETRICAL AND GYNECOLOGICAL SOCIETY

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

WASHINGTON GYNECOLOGICAL SOCIETY

PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY

OBSTETRICAL SOCIETY OF BOSTON

LOUISVILLE OBSTETRICAL AND GYNECOLOGICAL SOCIETY

SEATTLE GYNECOLOGICAL SOCIETY

ALABAMA ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS

AKRON OBSTETRICAL AND GYNECOLOGICAL SOCIETY

KANSAS CITY GYNECOLOGICAL SOCIETY

CENTRAL NEW YORK ASSOCIATION OF GYNECOLOGISTS AND  
OBSTETRICIANS

NEW JERSEY OBSTETRICAL AND GYNECOLOGICAL SOCIETY

IOWA OBSTETRIC AND GYNECOLOGIC SOCIETY

THE TEXAS ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS

OKLAHOMA CITY OBSTETRICAL AND GYNECOLOGICAL SOCIETY

MEMPHIS OBSTETRICAL AND GYNECOLOGICAL SOCIETY

UTAH OBSTETRICAL AND GYNECOLOGICAL SOCIETY

ROCHESTER OBSTETRICAL AND GYNECOLOGICAL SOCIETY

ARKANSAS OBSTETRICAL AND GYNECOLOGICAL SOCIETY

TENNESSEE STATE OBSTETRICAL AND GYNECOLOGICAL SOCIETY



## IN CONSTIPATION



"...Senokot  
can be given safely  
to women  
in the postpartum period  
because it is not  
excreted in the breast milk"

"The continued use of Senokot since the trial  
was completed has confirmed that it is a very  
satisfactory laxative for puerperal women."<sup>2</sup>

'Senokot' is documented by the fastest-growing bibliography on constipation correction.

# *natural bowel corrective* **Senokot**<sup>®</sup> TABLETS/GRANULES

**TABLETS:** Small, easy to swallow. Dosage: For Adults—2 to 4 tablets nightly. For Children—1 to 2 tablets nightly. Supply: Bottles of 100. **GRANULES:** Deliciously cocoa-flavored. Dosage: For Adults—1 to 2 teaspoonfuls nightly. For Children—1/2 to 1 teaspoonful nightly. Supply: 8 and 4 ounce canisters.

1. Steigmann, F.: "Newer Drugs in the Therapy of Constipation" In Disturbances in Gastrointestinal Motility, ed. J. Alfred Rider and H. C. Moeller, Springfield, Ill., Charles C Thomas, 1959, p. 293. 2. Duncan, A. S.: Brit. M. J. No. 5016:439 (Feb. 23) 1957.

SENOKOT® BRAND OF STANDARDIZED CONCENTRATE OF TOTAL ACTIVE PRINCIPLES OF CASSIA ACUTIFOLIA PODS, PURDUE FREDERICK.



*The Purdue Frederick Company*

DEDICATED TO PHYSICIAN AND PATIENT SINCE 1892  
NEW YORK 14, N.Y. | TORONTO 1, ONTARIO

© COPYRIGHT 1960, THE PURDUE FREDERICK COMPANY.

## Editors

HOWARD C. TAYLOR, JR., *Editor in Chief*

JOHN I. BREWER, ALLAN C. BARNES, *Editors*

LOUIS M. HELLMAN, *Abstract and Book Review Editor*

ROBERT E. HALL, *Assistant Editor*

## Advisory committee on policy

Francis Bayard Carter  
Andrew Marchetti  
Daniel G. Morton  
Newell W. Philpott

Clyde L. Randall  
John Rock  
W. Norman Thornton

## Advisory editorial committee

Edward Allen  
Leroy A. Calkins  
Russell R. de Alvarez  
R. Gordon Douglas  
Louis M. Hellman  
Carl P. Huber  
Frank R. Lock  
Curtis J. Lund  
Charles E. McLennan  
Joe Vincent Meigs

William F. Mengert  
Norman F. Miller  
Ernest W. Page  
Franklin L. Payne  
Lawrence M. Randall  
Duncan E. Reid  
George V. Smith  
Wm. E. Studdiford  
Richard W. TeLinde  
Herbert F. Traut

---

*Give your patients  
the latest word*

# NINE MONTHS' READING

A Medical Guide for Pregnant Women

## The Author

**Robert E. Hall, M.D.**

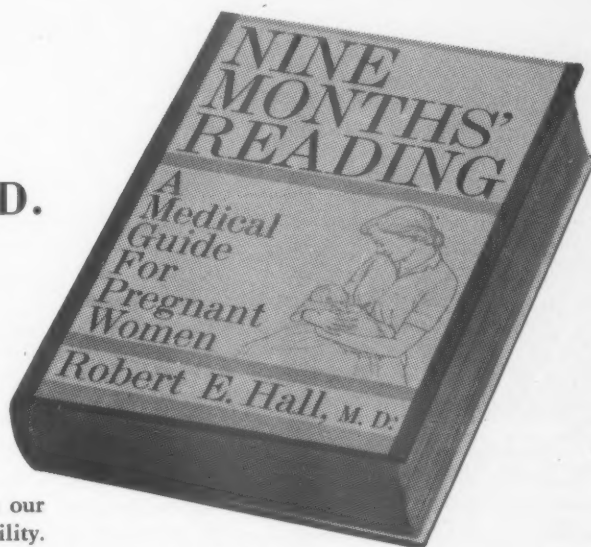
Assistant Clinical Professor of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons; Assistant Editor, *American Journal of Obstetrics and Gynecology* and *Bulletin of the Sloane Hospital for Women*.

"Dr. Hall is one of the ablest writers in our specialty and this book attests his ability. Here one will find many of the inevitable questions of the mother-to-be answered lucidly, and with common sense."—DR. ALLAN C. BARNES, Professor of Obstetrics and Gynecology, *Johns Hopkins University School of Medicine*.

## The Book:

A candid, comprehensive, and comprehensible discussion of every phase of pregnancy, childbirth, and early motherhood. Clear illustrations and up-to-date information on development of the fetus, symptoms and sensations, labor and delivery, complications, hospital procedures, breast feeding, and natural childbirth.

"Factual, informative and beautifully written. . . . In every respect this book covers the needs and desires of future parents."—DR. JOHN I. BREWER, *Professor of Obstetrics and Gynecology, Northwestern University Medical School*.



## Special Offer:

This is exactly the book to give to your patients. We will, therefore, be happy to send a FREE desk copy to all doctors who complete and return the coupon below. If, after you have examined NINE MONTHS' READING, you decide that you want to give copies to your patients, we will accept orders of 10 copies or more at a special 33⅓% discount, making a net price of \$1.97 per copy. The regular bookstore price of NINE MONTHS' READING is \$2.95.

DOUBLEDAY & COMPANY, INC.  
Dept. JO-6, Garden City, New York

- ☐ Please send me a FREE copy of NINE MONTHS' READING
- ☐ Please send me \_\_\_\_\_ copies (10 or more) at \$1.97 each
- ☐ Payment enclosed      ☐ Please bill me

NAME \_\_\_\_\_

ADDRESS \_\_\_\_\_

CITY \_\_\_\_\_ ZONE \_\_\_\_\_ STATE \_\_\_\_\_

# American Journal of Obstetrics and Gynecology

**Editors** Howard C. Taylor, Jr., *Editor in Chief*  
622 West 168th St., New York 32, New York

John I. Brewer, *Editor*  
303 East Chicago Ave., Chicago 11, Illinois

Allan C. Barnes, *Editor*  
725 N. Wolfe St., Baltimore 5, Maryland

**Publisher** The C. V. Mosby Company  
3207 Washington Blvd., St. Louis 3, Missouri  
Entered at the Post Office at St. Louis, Mo., as Second-Class Matter

## Business Communications

**Business Communications.** All communications in regard to advertising, subscriptions, changes of address, etc., should be addressed to the publishers, The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Missouri.

**Subscription Rates.** United States and its Possessions \$15.00 a year; Canada, Latin America, and Spain \$16.00; Other Countries \$17.50. Special rate for medical students and physicians on internship or residency programs, one half of the domestic rate; for students in other countries, one half of the domestic rate plus the full amount of the applicable charge for international postage. Single copies \$2.50 postpaid. Remittances for subscription should be made by check, draft, post office or express money order, payable to this Journal.

**Publication Order.** The monthly issues of this Journal form two semi-annual volumes; the index is in the last issue of the volume—in the June and December issues.

**Change of Address Notice.** Six weeks' notice is required to effect a change of address. Kindly give the exact name under which a subscription is entered and the full form of both old and new addresses, including the post office zone number.

**Advertisements.** Only products of known scientific value will be given space. Forms close first day of month preceding date of issue. Advertising rates and page sizes will be given on application.

**Bound Volumes.** Publishers' Authorized Bindery Service, 5811 West Division Street, Chicago 51, Illinois, will quote prices for binding complete volumes in permanent buckram.

*Published monthly.*  
*Subscriptions may begin*  
*at any time.*

## Editorial Communications

**Submission of Contributions.** Manuscripts should in general be sent to a particular Editor, according to the following plan: If it was read before one of the sponsoring societies or comes from abroad, to Dr. Howard C. Taylor, Jr.; if its source is from the Northeast, to Dr. Allan C. Barnes; if from the South, Middle West, or West, to Dr. John I. Brewer. The contributor may, however, if he wishes, address his manuscript to any Editor of his selection, but the editorial staff reserves the right to reassign papers from any source among themselves. Members of the Advisory Editorial Committee may be consulted by the Editors upon suitability of papers submitted for publication.

All articles published in this Journal must be contributed to it exclusively. If subsequently printed elsewhere (except in a volume of Society Transactions) due credit shall be given for original publication. The Editors expect all contributions to conform strictly to this rule.

It is assumed by the Editors that articles emanating from a particular institution are submitted with the approval of the requisite authority.

Neither the Editors nor the Publishers accept responsibility for the views and statements of authors as published in their original communications.

**Manuscripts.** Manuscripts should be typewritten on one side of the paper only, with double spacing and liberal margins. References should be placed at the end of the article and should conform to the style of the Quarterly Cumulative Index Medicus, viz., name of author, name of periodical, volume, page, and year. Illustrations accompanying manuscripts should be numbered, provided with suitable legends, and marked lightly on the back with the author's name. Authors should indicate on the manuscript the approximate position of tables and text figures.

**Illustrations.** A reasonable number of halftone illustrations will be reproduced free of cost to the author, but special arrangements must be made with the Editors for color plates, elaborate tables, or extra illustrations. Copy for zinc cuts (such as pen drawings and charts) must be drawn and lettered in India ink or black typewriter ribbon (when the typewriter is used). Only good glossy photographic prints should be supplied for halftone work; original drawings, not photographs of them, should accompany the manuscript.

**Announcements.** Announcements of meetings must be received by the Editors at least 2½ months before the time of the meeting.

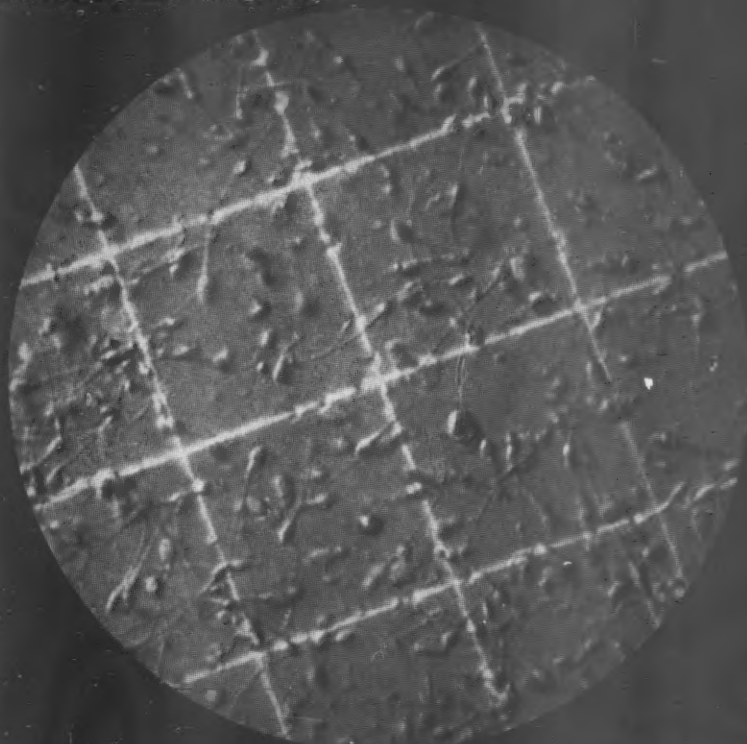
**Exchanges.** Contributions, letters, exchanges, reprints, and all other communications relating to the Abstract section of the Journal should be sent to Dr. Louis M. Hellman, State University of New York, College of Medicine, 451 Clarkson Ave., Brooklyn 3, New York.

**Review of Books.** Books and monographs, native and foreign, on obstetrics, gynecology, and abdominal surgery will be reviewed according to their merits and the space at disposal. Send books to Dr. Louis M. Hellman, State University of New York, College of Medicine, 451 Clarkson Ave., Brooklyn 3, New York.

**Reprints.** Reprints of articles must be ordered from the Publishers, The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Missouri, who will send their schedule of prices. Individual reprints of an article must be obtained through the author.



IN CONTRACEPTION...



## WHY IS DIFFUSION IMPORTANT?

Because the active ingredients of a spermicidal preparation must diffuse rapidly into the seminal clot and throughout the vaginal canal to be clinically effective. Lanesta Gel offers this *dual* protection. Its four spermicidal agents quickly invade the clot to stop the main body of sperm. It spreads evenly and quickly throughout the vaginal canal—seeks out every wrinkle and fold that may offer concealment to sperm. With this rapid diffusion, your patient receives full benefit of the swift spermicidal action of Lanesta Gel — in minutes — a decisive measure in conception control.

In Lanesta Gel 7-chloro-4-indanol, a new, effective, nonirritating, nonallergenic spermicide, produces immediate immobilization of spermatozoa in dilution

of up to 1:4,000. The addition of 10 per cent NaCl in ionic form greatly accelerates spermicidal action. Ricinoleic acid facilitates rapid inactivation and immobilization of spermatozoa and sodium lauryl sulfate acts as a dispersing agent and spermicidal detergent.

Lanesta Gel with a diaphragm provides one of the most effective means of conception control. However, whether used with or without a diaphragm, the patient and you, doctor, can be certain that Lanesta Gel provides faster spermicidal action — plus essential diffusion and retention of the spermicidal agents in a position where they can act upon the spermatozoa.



# new Lanesta® Gel

Supplied: Lanesta Exquiser® . . . with diaphragm of prescribed size and type; universal introducer; Lanesta Gel, 3 oz. tube, with easy clean applicator, in an attractive purse. Lanesta Gel, 3 oz. tube with applicator; 3 oz. refill tube — available at all pharmacies.

A product  
of Lanteen®  
research.

Manufactured by Esta Medical Laboratories, Inc., Alliance, Ohio. Distributed by GEORGE A. BREON & CO., New York 18, N. Y.

# **Proven**

in over five years of clinical use  
and more than  
750 published clinical studies

# **Effective**

**FOR RELIEF OF ANXIETY  
AND TENSION**

# **Outstandingly Safe**

# **Miltown®**

*Usual dosage: One or two 400 mg. tablets t.i.d.  
Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets;  
or as MEPROTABS\*—400 mg. unmarked, coated tablets.*

\*Trade-mark

CM-2087

- 1 simple dosage schedule produces rapid, reliable tranquilization without unpredictable excitation
- 2 no cumulative effects, thus no need for difficult dosage readjustments
- 3 does not produce ataxia, change in appetite or libido
- 4 does not produce depression, Parkinson-like symptoms, jaundice or agranulocytosis
- 5 does not impair mental efficiency or normal behavior

**Miltown<sup>®</sup>**  
meproamate (Wallace)

 WALLACE LABORATORIES / *New Brunswick, N. J.*

Preserving the Surgeon's Finest Skill  
Through Even the Longest Procedures



**Amsco**  
**SURGICAL**  
**CHAIR**



The relaxed comfort and good posture support provided by the Amsco Surgical Chair minimize the strain of physical fatigue, permitting the surgeon or the anesthesiologist to concentrate his full energy upon the patient and the procedure.

The spring tension of the swivel seat and the height of the backrest are easily adjustable to provide comfort and correct support for each individual.

Height and mobility of the chair are controlled by

the surgeon himself from a sitting position . . . without violating the sterile field. Hydraulic pump foot pedals raise or lower the chair to any desired point in the 19½" to 27½" range. The entire chair moves smoothly on casters which are specially designed to avoid picking up sutures. It locks in position with a kick pedal which lowers or raises the center post anchor.

Seat, backrest and casters are covered with conductive rubber.

Write for illustrated brochure MC-559

World's largest designer and manufacturer of  
Sterilizers, Surgical Tables, Lights and Related Equipment



**AMERICAN**  
**STERILIZER**

ERIE • PENNSYLVANIA



women of childbearing age...  
and growing children...

are  
depleting their  
iron  
reserves

Iron deficiency anemias occur most often among women of childbearing age and growing children. Unless extra iron is provided, children's high growth requirements and women's iron loss from menstruation may dangerously deplete iron reserves. Many clinicians regularly prescribe a hematinic for six weeks each year during a woman's reproductive years. Children and adolescents are kept on intermittent iron therapy.

Livitamin, with peptonized iron and B complex, provides effective iron therapy with minimal side effects. Unlike many hematinics, Livitamin is pleasant tasting and well tolerated. Peptonized iron has as high a rate of absorption and storage, and is much less irritating than ferrous sulfate. B complex and other ingredients provide integrated nutritional support.

# LIVITAMIN<sup>®</sup>

with Peptonized Iron

## FORMULA Each Peduncle contains:

Iron peptonized (Equiv. in elemental iron to 1 mg.)	420 mg.	Nicotinamide	50 mg.
Manganese citrate, soluble	155 mg.	Pyridoxine hydrochloride	1 mg.
Thiamine hydrochloride	10 mg.	Pantothenic acid	5 mg.
Riboflavin	10 mg.	Liver fraction 1	2 Gm.
Vitamin B <sub>12</sub> Activity (Derived from Cobalamin conc.)	20 mcg.	Wise Bran extract	1 Gm.
		Inositol	30 mg.
		Choline	50 mg.

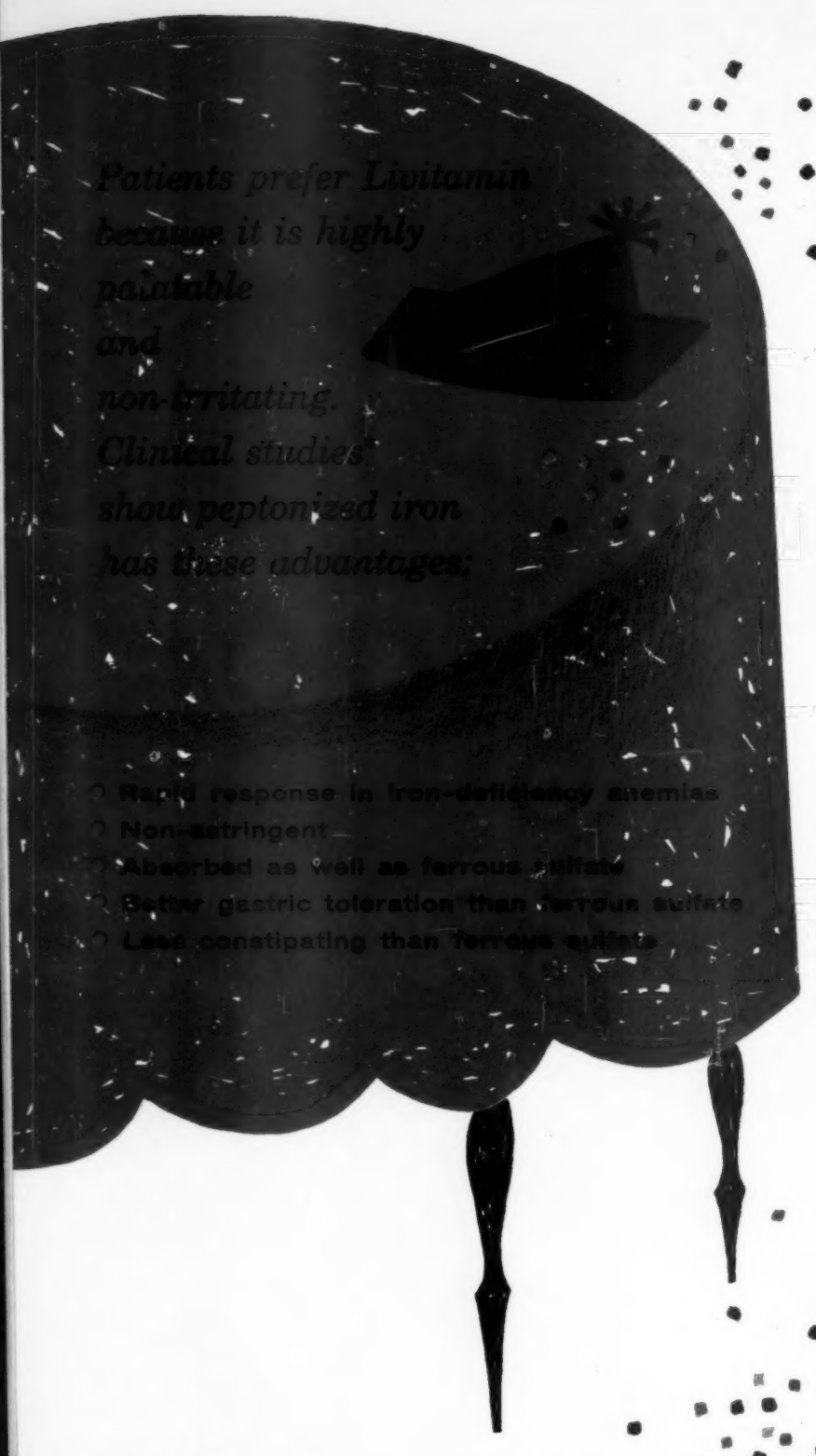
SUPPLIED IN LIQUID OR CAPSULE

THE S. E. M ASSENGILL COMPANY

Boston, Springfield • New York  
Kansas City • San Francisco

with-  
foot  
point  
moves  
igned  
with  
post  
  
with

AN  
ER  
ANIA



*Patients prefer Livitamin  
because it is highly  
palatable  
and  
non-irritating.*

*Clinical studies  
show peptonized iron  
has these advantages:*

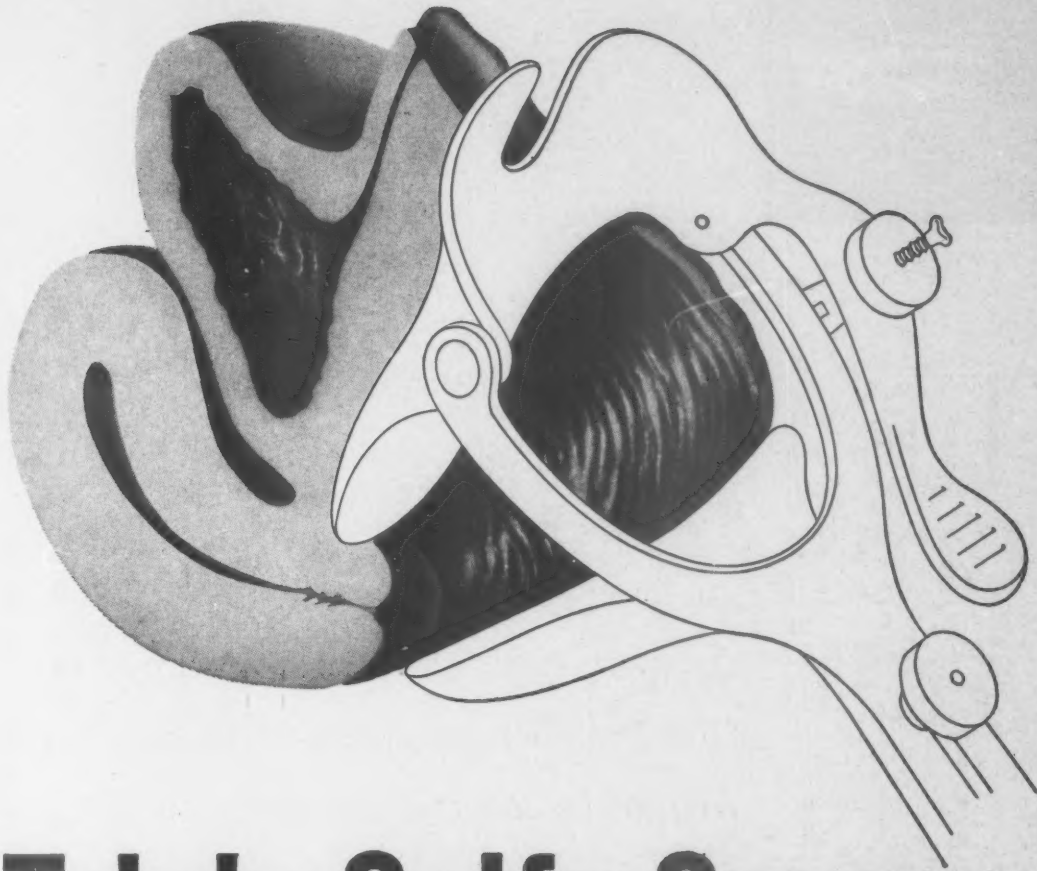
- Rapid response in iron-deficiency anemias
- Non-astringent
- Absorbed as well as ferrous sulfate
- Better gastric toleration than ferrous sulfate
- Less constipating than ferrous sulfate

# LIVITAMIN<sup>®</sup> *with Peptonized Iron*

... the preferred  
hematinic

\*Keith, J.H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate, Am. J. Clin. Nutrition 1:35 (Jan.-Feb., 1957).

THE S. E. **M**ASSENGILL COMPANY Bristol, Tennessee • New York • Kansas City • San Francisco



# Triple Sulfa Cream

TRADEMARK

- in mixed vaginal infections
- against secondary invaders  
in trichomoniasis
- in postpartum care
- after vaginal surgery







When  
there's  
a pram  
in her  
future,

She *knows*. And the moment is bright. Now...  
to preserve her serenity throughout the coming  
months. ■ One way is to make sure mother-  
to-be is getting the right kind of nutritional  
support—such as that provided by Pramilets.  
For Pramilets complement the sound dietary  
regimen you'll give your pregnant patient with:  
(1) phosphorus-free calcium; (2) well-tolerated  
iron, in the form of ferrous fumarate; and (3) the  
other essential vitamins and minerals. ■ Your patient will be grateful, too,  
for Pramilets' easy dosage schedule. In most cases, a  
Filmtab a day is all that's needed to carry her through  
term. ■ As for a reminder to take her daily supple-  
ment, the slim, graceful Table  
Bottle will take care of that.

she'll  
need  
Pramilets®

*Comprehensive vitamin-mineral support with just 1 Filmtab daily.*

Pramilets—Abbott's Phosphorus-free Prenatal Supplement.  
Filmtab—Film-sealed Tablets, Abbott; U.S. Pat. No. 2,881,085.



006245



.. today





## **A brighter "Good morning!"**

### **No complaints about**

- \* post-episiotomy,
- \* tender hemorrhoids,
- \* or fissured nipples when you prescribe

## *Americaine*<sup>®</sup> **Topical Anesthetic**

Americaine relieves surface discomfort quickly, sustains relief up to six hours with a single application—because only Americaine contains 20% dissolved benzocaine.

What about sensitivities? None reported in over 11,800 published clinical cases<sup>1</sup>...negligible incidence in 10 years' steadily growing use.

### **Americaine Aerosol**

For quick spray application. Available in 3 oz. prescription size, and 5.5 oz. and 11 oz. dispensers.

### **Americaine Ointment**

For simple manual application. Available in 1 oz. tube w/applicator.

1. References on request.



**ARNAR-STONE LABORATORIES, INC.,** Mount Prospect, Ill.



*thanks to*  
**DESITIN<sup>®</sup>**  
hemorrhoidal  
**SUPPOSITORIES**  
*with cod liver oil*


*Samples* and literature available from

**DESITIN CHEMICAL COMPANY • 812 Branch Ave., Providence 4, R. I.**









when reassurance  
is not enough...

**Ritalin**<sup>®</sup>  
helps brighten the day

**Clinicians report how  
RITALIN gives  
dispirited patients  
a lift... with safety**

"These patients represented the types of cases which might come into any doctor's office for treatment... the chronically ill and incurables, the convalescing group, the 'low' patients, depressed because of pressure of present-day living, and the group who were on medications which caused depressed states."

"The effect [of Ritalin] lasted about four hours, gave the patient a feeling of well-being and that life was worth living. Their worries seemed to disappear; they were alert, fatigue disappeared, and they could go all day without tiring. The effects gradually disappeared with no extreme let-down or rebound effect."

"... the drug [Ritalin] had no effect on blood pressure, the blood count, urine or blood sugar, did not depress the appetite, and produced no tachycardia. There was no evidence of any allergic manifestations in any of the cases."

—Natenshon, A. L.: Dis. Nerv. System 17:392 (Dec.) 1956.

"A double blind study of the mood elevating properties of Ritalin<sup>®</sup> in 112 patients showed statistically significant effect. ... This drug offers great help in patients in whom elevation of the mood is desirable."

—Landman, M. E., Preisig, R., and Perlman, M.: J. M. Soc. New Jersey 55:55 (Feb.) 1958.

"It [Ritalin] causes mild depressions to vanish. ... It changes dull, apathetic patients into more alert, interested ones."

"It stimulates apathetic and negativistic patients to more normal, productive activity."

—Pennington, V. M.: Mississippi Doctor 35:57 (Aug.) 1957.

Complete information available on request.

SUPPLIED: TABLETS, 5 mg. (yellow), 10 mg. (light blue), 20 mg. (peach-colored)

RITALIN<sup>®</sup> hydrochloride  
(methylphenidate  
hydrochloride CIBA)

**CIBA**  
SUMMIT, NEW JERSEY

2/2776MK

# FOR **P**ROVEN **M**ENOPAUSAL **B**ENEFITS with extra relief from anxiety and tension

The vast majority of menopausal women, *especially on the first visit*, are nervous, apprehensive, and tense. PMB-200 or PMB-400 gives your patient the advantage of *extra* relief from anxiety and tension, particularly when the patient is "high strung," under prolonged emotional stress, or when psychogenic manifestations are acute. Proven menopausal benefits are confirmed by the wide clinical acceptance of

"Premarin," specifically for the relief of hot flushes and other symptoms of estrogen deficiency, together with the well established tranquilizing efficacy of meprobamate.

Two potencies to meet the needs of your patients:

# PMB 200

"PREMARIN® WITH MEPROBAMATE"

PMB-200—Each tablet contains conjugated estrogens equine ("Premarin") 0.4 mg., and 200 mg. of meprobamate. When greater tranquilization is necessary you can prescribe PMB-400—Each tablet contains conjugated estrogens equine ("Premarin") 0.4 mg., and 400 mg. of meprobamate. Both potencies are available in bottles of 60 and 500.

AYERST LABORATORIES  
New York 16, N.Y., Montreal, Canada



MEPROBAMATE, LICENSED UNDER U. S. PAT. NO. 2,724,720. 551F

# Cystitis

*Responds  
Rapidly  
to Soothing,  
Antiseptic*

## URISED®



Effective as individual therapy or as adjunctive medication in your regimen

**SIMPLE, ACUTE or CHRONIC** infections of the urinary tract are *safely* treated with URISED\*. In 50 geriatric cases (average age 75½ years) Strauss reports<sup>1</sup> excellent to good results in 72%. No drug reactions occurred during prolonged therapy even though the majority of cases suffered from some form of chronic cardiac, vascular or neurologic disease.

New, additional evaluations confirm<sup>2,3</sup> these findings.

Each Urised tablet contains: atropine sulfate 1/2000 gr.; hyoscyamine 1/2000 gr.; gelsemium, methenamine, methylene blue, benzoic acid, salol.

Rx URISED: Two Tablets, q.i.d.

REFS.: 1. Strauss, B., Clinical Med., 4:307-310, 1957; 2. Marshall, W., Clin. Med., Mar., 1960; 3. Haas, J., Pers. Com.

### PAIN RELIEF IS PROMPT SINCE URISED:

- relaxes smooth muscle spasm, overcoming urinary retention, • attacks infection with bacteriostatic-spasmolytic actions, • effects results in either acid or alkaline media.

### PHYSICIANS AND PATIENTS ARE INCREASINGLY GRATIFIED BECAUSE URISED:

- is safe, causes no undesirable reactions, • prevents development of "resistant strains," • has no contraindications, • IS ECONOMICAL.



*\*For generous free treatment table supplies of Urised startersamples, just mail the card with your name and address on the reverse side.*

Postage  
Will Be Paid  
by  
Addressee

No  
Postage Stamp  
Necessary  
If Mailed in the  
United States

**BUSINESS REPLY CARD**

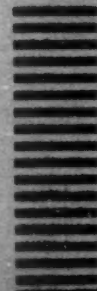
FIRST CLASS PERMIT NO. 9170, CHICAGO, ILL.

**CHICAGO PHARMACAL COMPANY**

5547 N. Ravenswood Ave.

Uptown Station

CHICAGO 40, ILL.





# Pleased Menopausal Patients are Routine with **ESTROSED** Therapy

Estrogenic deficiencies and emotional disturbances are successfully managed with flexible, potent Estrosed.

- Vasomotor instabilities respond to ethinyl estradiol, "... one of the most potent estrogens known."<sup>1</sup>
- Nervousness and insomnia are quieted with reserpine, "... useful chiefly for its psychotherapeutic sedative action in the symptomatic management of patients with anxiety or tension psychoneurosis . . ."<sup>2</sup>

Your results with Estrosed therapy will also be gratifying. Estrosed contains 0.01 mg. ethinyl estradiol and 0.1 mg. reserpine.

## *Low Dosage—Economical Therapy*

Suggested dosage: one or two tablets once or twice daily for one week or until symptoms are controlled. For maintenance, one or two tablets daily or every other day.

1. N.N.R., 1959, 515 2. Ibid, 376



Chicago Pharmacal Co.  
5547 N. Ravenswood Ave.  
Chicago 40, Ill.

OG-JRL

Re: Please forward generous supplies of Urised ☐ Estrosed ☐

Dr. \_\_\_\_\_

Address \_\_\_\_\_

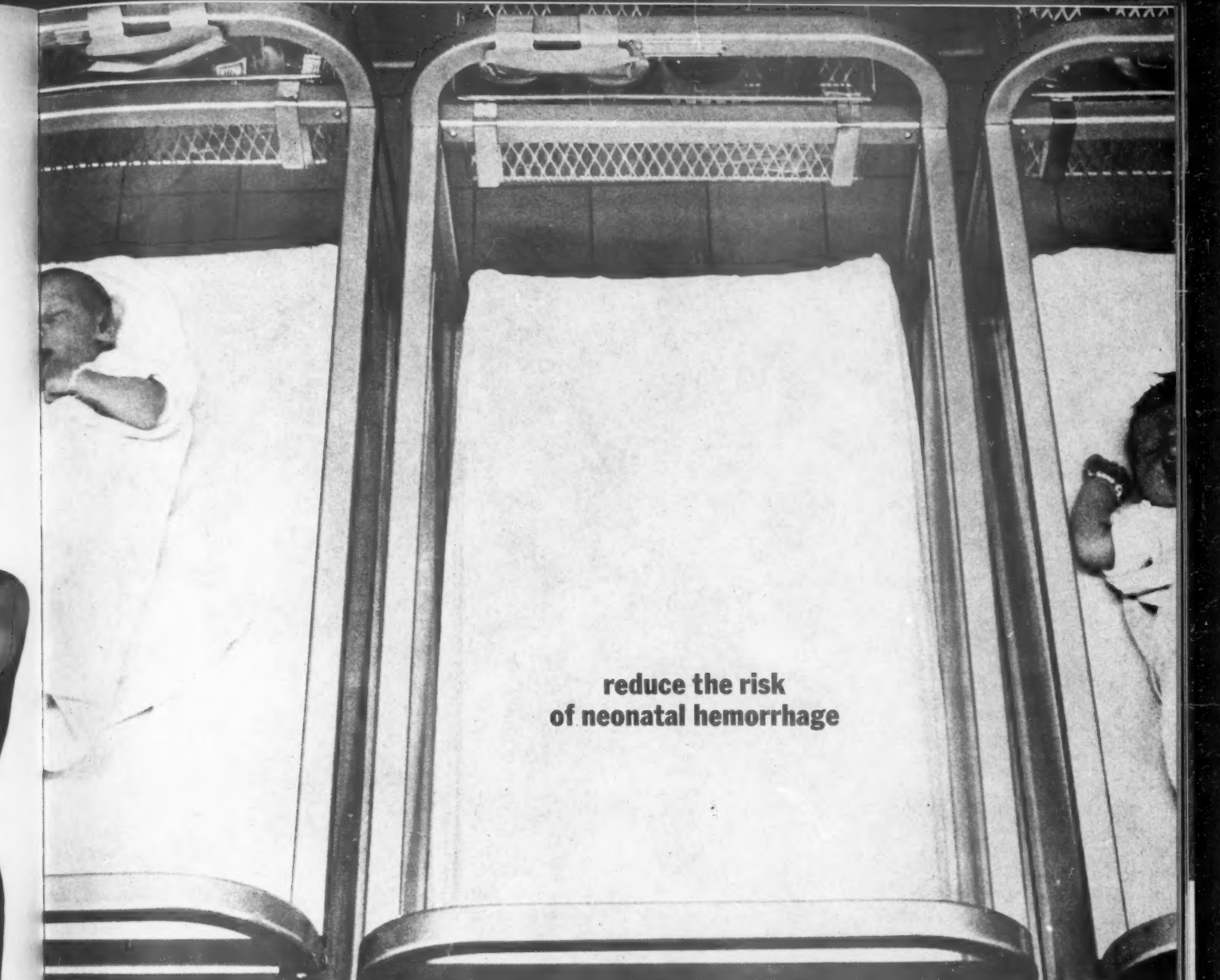
City \_\_\_\_\_ State \_\_\_\_\_

*For generous supplies of Estrosed and Urised for use as "starter treatments" fill out and return this card.*



**CHICAGO  
PHARMACAL  
COMPANY**





**reduce the risk  
of neonatal hemorrhage**

# Mephyton<sup>®</sup>

vitamin K<sub>1</sub>


**"has a more prompt, more potent and more prolonged effect than the vitamin K analogues"\***

- helps prevent hypoprothrombinemia, the most common cause of neonatal hemorrhage
- helps reduce incidence of intracranial hemorrhage due to hypoprothrombinemia

*Supply:* Tablets 5 mg.; bottles of 100. Emulsion, 1-cc. ampuls containing 10 mg. and 50 mg. per cc.; boxes of 6 ampuls.

*For additional information, write Professional Services, Merck Sharp & Dohme, West Point, Pa.*

\*Council on Drugs: New and Nonofficial Drugs, Philadelphia, J. B. Lippincott Co., 1959, p. 661.

 **MERCK SHARP & DOHME**, DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

MEPHYTON IS A TRADEMARK OF MERCK & CO., INC.





*while  
she's  
waiting,  
doctor...*

She has so many questions. When she inquires about infant feeding, you want to prescribe a formula that meets the highest known nutritional standards and closely resembles breast milk. You want a formula optimal in proteins, fats, carbohydrates, vitamins and minerals to promote sound health and physiologic growth.

The S-M-A Formula, made by Wyeth, is a nutritionally balanced food patterned after breast milk. Your patients will appreciate its convenience...ease of use...and economy of time and money.

"Expecting Your Baby," the new Wyeth booklet, helps answer her many questions. It's a handsome, factual guide for expectant mothers through the prenatal period. Your Wyeth Territory Manager will be glad to supply you with copies.

Wyeth Laboratories Philadelphia 1, Pa.

INSTANT POWDER

CONCENTRATED LIQUID



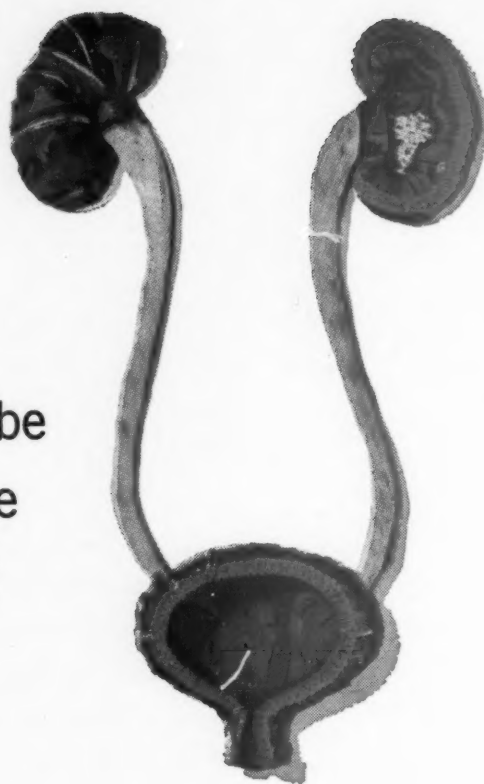
A Century of Service to Medicine

**S-M-A<sup>®</sup>**

**Food Formula For Infants**

UNSURPASSED IN NEARNESS TO HEALTHY MOTHERS' MILK

Just a "simple"  
case of cystitis  
may be the  
precursor of  
pyelonephritis<sup>1</sup>—  
or may actually be  
the first evidence  
of a pre-existing  
pyelonephritic  
process.<sup>2</sup>



WHEN TREATING CYSTITIS—SPECIFY

**FURADANTIN<sup>®</sup>**

brand of nitrofurantoin

FIRST

to ensure rapid control of infection  
throughout the urogenital system

Rapid bactericidal action against a wide range of gram-positive and gram-negative bacteria including organisms such as staphylococci, *Proteus* and certain strains of *Pseudomonas*, resistant to other agents

- actively excreted by the tubule cells in addition to glomerular filtration
- negligible development of bacterial resistance after 8 years of extensive clinical use
- excellent tolerance—nontoxic to kidneys, liver and blood-forming organs
- safe for long-term administration

**AVERAGE FURADANTIN ADULT DOSAGE:** 100 mg. q.i.d. with meals and with food or milk on retiring. Supplied: Tablets, 50 and 100 mg.; Oral Suspension, 25 mg. per 5 cc. tsp.

**REFERENCES:** 1. Campbell, M. F.: *Principles of Urology*, Philadelphia, W. B. Saunders Co., 1957. 2. Colby, F. H.: *Essential Urology*, Baltimore, The Williams & Wilkins Co., 1953.

**NITROFURANS**—a unique class of antimicrobials—neither antibiotics nor sulfonamides

EATON LABORATORIES, NORWICH, NEW YORK





## off to a good day—constipation relieved

Pleasant-tasting Agoral is the laxative virtually tailor-made for busy people. Taken at bedtime, Agoral works effectively and gently overnight, without disturbing sleep, to produce a normal bowel movement the next morning—*before* the day's activities begin.

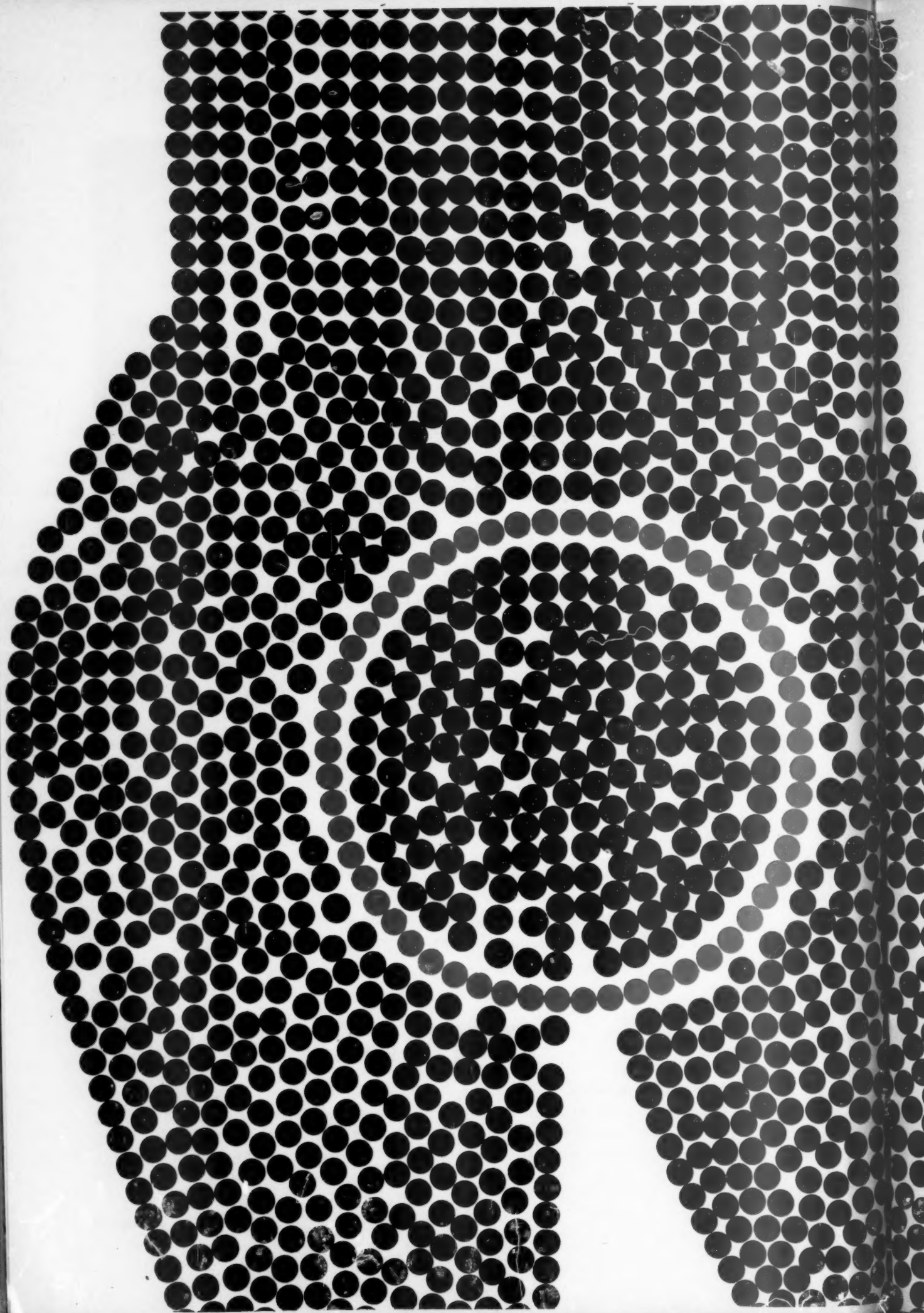
# agoral®

*the gentle laxative*



MORRIS PLAINS, N.J.

AG-M502



# CONSISTENT RESPONSE IN VAGINITIS

## UNREMITTING THERAPY FOR PERSISTENT SYMPTOMS

**85% SUCCESS;<sup>1,2</sup> TRIBURON VAGINAL CREAM**  
ACHIEVED SYMPTOMATIC CONTROL IN 109 OF 128  
WOMEN WITH TRICHOMONAL, MONILIAL AND NON-  
SPECIFIC VAGINITIS. PARTICULARLY GOOD RESULTS  
WERE OBTAINED IN TRICHOMONAL AND MIXED  
INFECTIONS, AND ONLY TWO INSTANCES OF TRANSIENT  
BURNING OCCURRED. OF 106 CASES FOLLOWED FOR  
THREE MONTHS, ONLY 11 RECURRENCES WERE NOTED.

IN ONE STUDY, TRIBURON VAGINAL CREAM  
DEMONSTRATED "DEFINITE ADVANTAGES"<sup>1</sup> OVER  
OTHER PREPARATIONS: HIGH ANTIBACTERIAL AND  
ANTITRICHOMONAL EFFECTS, RAPID DIFFUSION,  
PROLONGED RETENTION. FURTHER, THE ACTIVE  
COMPONENT OF TRIBURON VAGINAL CREAM,  
TRICLOBISONIUM CHLORIDE, HAS BEEN PROVED  
"NON-IRRITATING...NOT SENSITIZING."<sup>3</sup>

TRIBURON VAGINAL CREAM FOR VULVITIS AND  
VAGINITIS DUE TO TRICHOMONAS VAGINALIS,  
CANDIDA ALBICANS, HEMOPHILUS VAGINALIS AS  
WELL AS MIXED INFECTIONS; AFTER CAUTERIZATION,  
CONIZATION AND IRRADIATION; FOR SURGICAL  
AND POSTPARTUM TREATMENT. THERAPY MAY BE  
CONTINUED DURING PREGNANCY AND MENSTRUATION.

## HIGHLY ACCEPTABLE TO PATIENTS

TRIBURON VAGINAL CREAM—A SMOOTH, WHITE,  
NONSTAINING PREPARATION WITH NO HINT OF  
MEDICINAL ODOR—HAS THE ADVANTAGES  
OF CONVENIENT BEDTIME ADMINISTRATION AND  
OF DISPOSABLE APPLICATORS.

SUPPLIED: 3-OUNCE TUBES WITH 18 DISPOSABLE APPLICATORS.

REFERENCES: 1. N. MULLA AND J. J. McDONOUGH, ANN. NEW YORK ACAD. SC., 82:  
(ART. 1), 182, 1959. 2. L. E. SAVEL, D. B. GERSHENFELD, J. FINKEL AND P.  
DRUCKER, IBID., P. 186. 3. R. C. V. ROBINSON AND L. E. HARMON, ANTIBIOTICS  
ANNUAL 1958-1959, NEW YORK, MEDICAL ENCYCLOPEDIA, INC., 1959, P. 113.

TRIBURON® CHLORIDE



ROCHE LABORATORIES

DIVISION OF HOFFMANN-LA ROCHE INC • NUTLEY 10, N. J.

# Triburon

## VAGINAL CREAM

decisive microbicidal therapy in a delicate matter  
not an antibiotic • not a nitrofurantoin



**Factual Clinical Data:** Male, 65, with dislocated shoulder; patient in great pain. Fifteen minutes after administration of 10 cc. of ROBAXIN Injectable, dislocation reduced on first attempt, and patient was able to move arm easily. Photographs used with patient's permission.



For prompt, prolonged,  
pain-free relaxation of  
skeletal muscle spasm—  
without drowsiness...

# Robaxin<sup>®</sup>



Methocarbamol 'Robins' U.S. Pat. No. 2770649

**ROBAXIN Injectable:** for relaxation of painful spasm within minutes.

**ROBAXIN Tablets:** for initial relief, or to maintain relaxation originally induced by ROBAXIN Injectable. Virtually free from adverse side effects, including drowsiness.

Ten published studies show ROBAXIN Injectable and ROBAXIN Tablets beneficial in 91% of cases.<sup>1-10</sup> Literature available to physicians on request.

**SUPPLY:** ROBAXIN Tablets, 0.5 Gm. (white, scored) in bottles of 50 and 500.

ROBAXIN Injectable, each ampul containing 1.0 Gm. of methocarbamol in 10 cc. of sterile solution.

**A. H. ROBINS CO., INC., Richmond 20, Virginia**

Making today's medicines with integrity . . . seeking tomorrow's with persistence

**REFERENCES:** 1. Carpenter, E. B.: Southern M. J. 51:627, 1958. 2. Forsyth, H. F.: J.A.M.A. 167:163, 1958. 3. Grisolia, A., and Thomson, J. E. M.: Clin. Orthopaedics 13:299, 1959. 4. Hujgins, A. F.: Clin. Med. 6:2324, 1959. 5. Lewis, W. B.: California Med. 90:26, 1959. 6. O'Doherty, D. S., and Shields, C. D.: J.A.M.A. 167:160, 1958. 7. Park, H. W.: J.A.M.A. 167:168, 1958. 8. Plumb, C. S.: Journal-Lancet 78:531, 1958. 9. Poppen, J. L., and Flanagan, M. E.: J.A.M.A. 171:298, 1959. 10. Schaubel, H. J.: Orthopaedics 1:274, 1959.



*the true specific  
for  
monilial vaginitis*

# GENTIA-JEL<sup>®</sup>

*CURES ARE QUICKER* Gentia-jel's unsurpassed monilia-killing power results in quicker cures and less recurrence. *IMMEDIATE RELIEF* This soothing jel provides fast, gratifying relief of vulvar itching and burning... destroys fungi and bacteria. *COMPLETE COVERAGE* Gentia-jel disperses completely over vaginal and cervical mucosa, penetrates into all folds and bathes the vulvar labia.



*start therapy  
with GENTIA-JEL  
... it works  
when others fail*

# GENTIA-JEL

*the true specific  
for monilial vaginitis*

Gentian violet is the most effective agent known for the destruction of *Monilla albicans*. Numerous nonstaining preparations have been used in treating vaginal moniliasis but have proven far less effective than gentian violet.

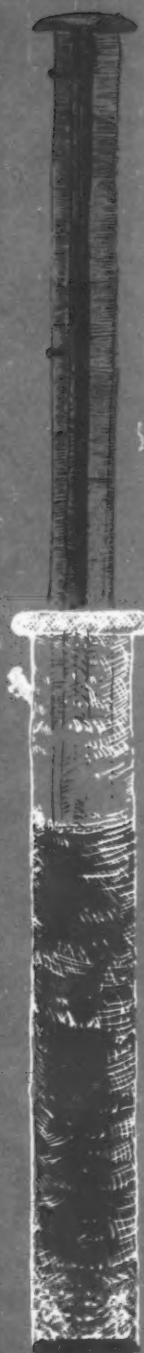
Gentia-jel's effectiveness is proved by its rate of cures during the last trimester of pregnancy, when mycotic infections are most difficult to cure. Gentia-jel is shown to be over 93% clinically effective, and has been used successfully in hundreds of cases refractory to other therapies.

Monillial reinfection is avoided with Gentia-jel by eliminating two major causes: (1) there is no manual introduction of tablets or suppositories into the vagina and (2) applicators are never re-used, but discarded.

And, Gentia-jel is easy for your patients to use. (1) Prior to retiring for the night, patients lie back with knees flexed, insert applicator and instill Gentia-jel. (2) Applicator is removed and discarded and a vaginal tampon or pledget of cotton is inserted in the introitus. A sanitary pad should be worn.

Treatment should be continued over 12 days to assure a negative smear.

Gentia-jel is supplied in packages of 12 single-dose disposable applicators.



**WHY WAIT UNTIL OTHER THERAPIES FAIL...  
START YOUR PATIENTS WITH GENTIA-JEL**

WESTWOOD PHARMACEUTICALS

Buffalo 13, New York

# Dulcolax<sup>®</sup>

brand of bisacodyl

## Suppositories

Solely by contact with the colonic mucosa, Dulcolax reflexly produces coordinated large bowel peristalsis with resulting evacuation.

Generally a single evacuation of soft, formed stool without catharsis or straining results.

"A gentle but effective laxative"\*  
In tablet form Dulcolax is eminently convenient when overnight action is required. For more prompt effect Dulcolax suppositories usually act within the hour.

\*Archambault, R.: Canad. M. A. J. 81:28, 1959.

Dulcolax<sup>®</sup>, brand of bisacodyl: yellow enteric-coated tablets of 5 mg. in box of 6 and bottle of 100; suppositories of 10 mg. in box of 6.

Under license from C. H. Boehringer Sohn, Ingelheim.

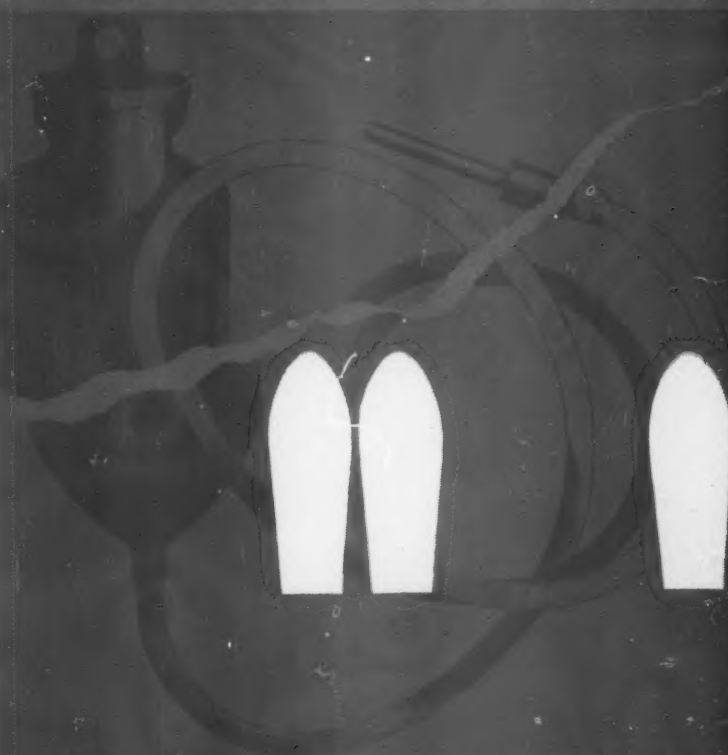


Geigy, Ardsley, New York

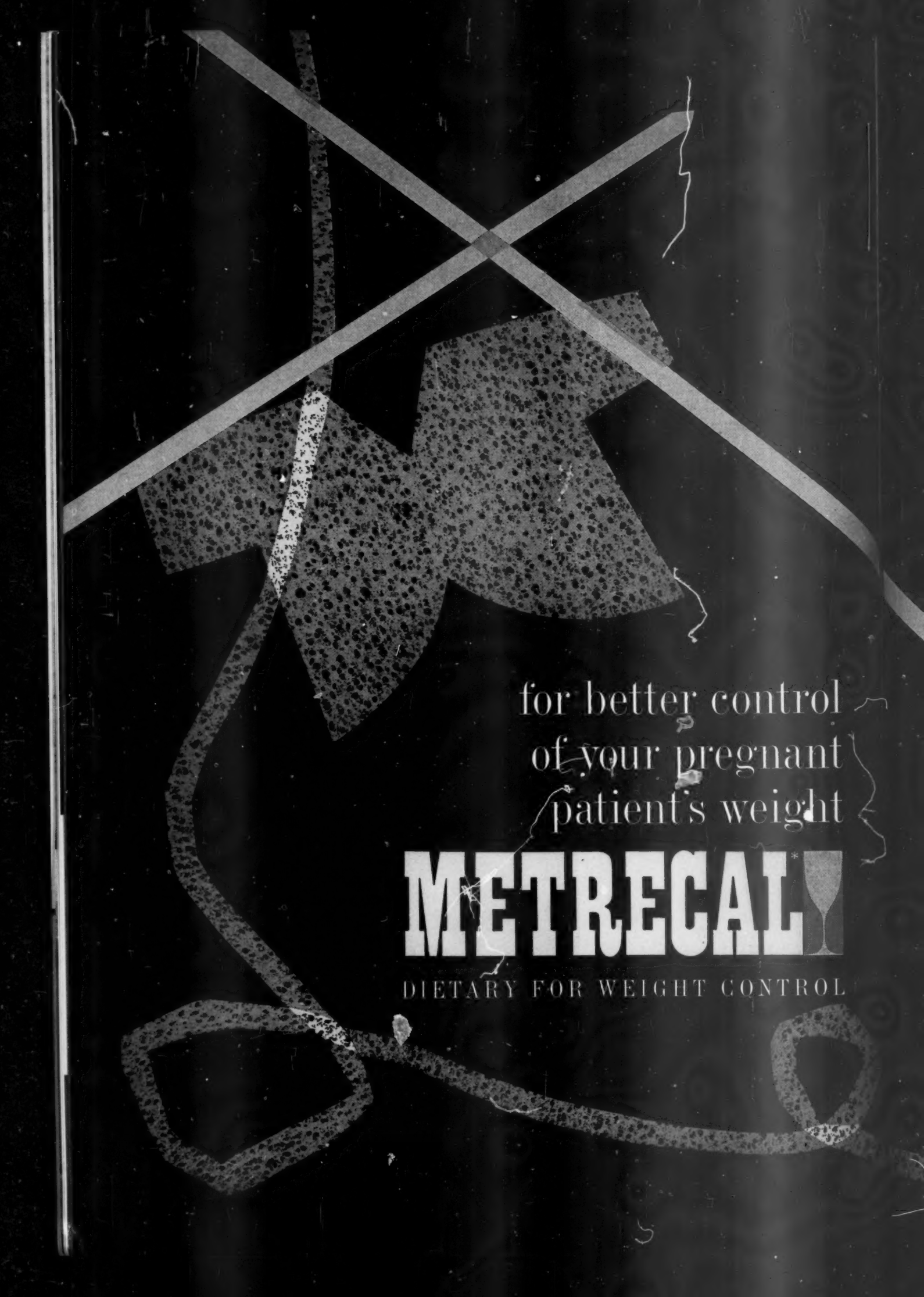
# Geigy

## circumventing the enema

unique contact laxative





An abstract graphic on a dark background. A large, light-colored 'X' is formed by two intersecting diagonal lines. In the center of the 'X' is a textured, irregular shape resembling a stylized flower or a piece of fabric. Below this, a long, thin, textured line winds across the lower half of the image, ending in two circular loops.

for better control  
of your pregnant  
patient's weight

**METRECAL\***

DIETARY FOR WEIGHT CONTROL



*measured calories to help keep your patients at optimal weight levels...without appetite depressants*

***sound nutrition with limited calories during pregnancy***

Metrecal may be used as the cornerstone around which to build a pregnancy diet when you wish to keep your patient's weight from rising too rapidly and to effect weight loss when necessary. A half-pound of Metrecal mixed with a quart of water supplies 900 calories in pleasant-tasting beverage form. This quantity provides 70 Gm. of protein, plus all essential vitamins and minerals. It is rich in calcium (2.0 Gm.) and iron (15 mg.). This daily ration may be divided into four glasses—one for each meal—and one at bedtime.

***highly flexible***

When substantial weight loss is indicated in pregnancy, Metrecal alone can provide the 900-calorie diet. Metrecal can also be used for one or two meals a day, as the total diet two or three days a week, or it may be used at meals with other foods. In the postpartum period, Metrecal provides an excellent method for losing weight or preventing additional weight gain.

***gratifying patient cooperation***

The high satiety, simplicity of use and palatability of Metrecal provide patients with a strong motivation to cooperate in weight-control programs.<sup>1,2</sup> Metrecal can provide a more dependable and nutritionally sound diet than the complex dietary schedules frequently used.

***no appetite depressants required***

Metrecal relies on sound nutritional principles for weight control rather than appetite depressants or diet "aids." Its pleasant taste and high satiety will help control the patient's appetite.

***easy to use—easy to prepare—variety of flavors***

All your patients do is mix Metrecal and water to a creamy, palatable smoothness with a blender, eggbeater or fork, refrigerate and serve. For variety in the diet, Metrecal is available in plain, chocolate and butterscotch flavors.

*Metrecal Weight-Control Guide* is available from your Mead Johnson Representative or by writing to us, Evansville 21, Indiana.

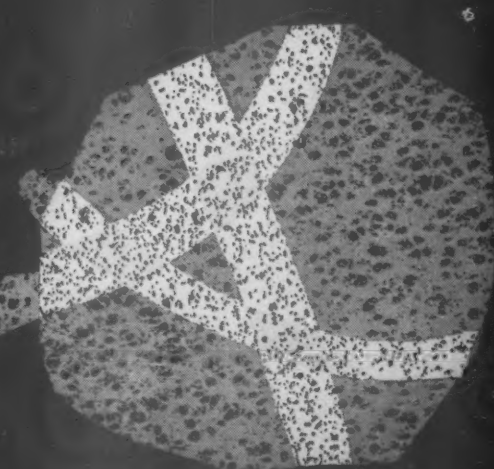
*References:* (1) Antos, R. J.: *Southwestern Med.*, 40:695-697 (Nov.) 1959. (2) Tullis, I. E., to be published.



**Mead Johnson**  
*Symbol of service in medicine*

© T.M.

89460



SMITH  
KLINE &  
FRENCH

# Compazine<sup>®</sup> Injection 5 mg./cc.

brand of prochlorperazine

1. beneficial calming action
2. prompt antiemetic effect
3. well tolerated by mother and infant

- hypotensive effect is minimal • minimal alteration of analgesic/anesthetic regimens due to lack of significant potentiation • may be given I.V., as well as I.M. • pain at site of injection has not been a problem

2 cc. Ampuls\*—boxes of 6 and 100. 10 cc. Multiple-dose Vials\*—boxes of 1 and 20.

\*Also available in special hospital packages. Additional information on request.

BEFORE,  
DURING,  
OR AFTER  
LABOR AND  
DELIVERY



for your  
obstetrical  
and  
gynecological  
patient

## BACULIN

VAGINAL TABLETS

FUNGICIDAL . . . BACTERICIDAL . . . PROTOZOICIDAL COMPREHENSIVE  
TREATMENT OF VAGINAL INFESTATION.

*A single BACULIN vaginal tablet generally destroys the causes of vaginitis, namely Trichomonas Vaginalis, Candida Albicans, and non-specific organisms. Prescribe BACULIN vaginal tablets in your next case of non-venereal vaginitis.*

## desplex

ANTIABORTIVE

ACCIDENTS OF PREGNANCY CAN NOT BE CURED. THEY MUST BE PREVENTED.  
desplex IS A CLINICALLY PROVED ANTIABORTIVE.

*desplex, a unique combination of ultramiconized diethylstilbestrol and vitamins C, and B complex, was shown 96% effective in carrying 1200 difficult pregnancies to term.<sup>1</sup> For assurance of a successful pregnancy, prescribe desplex tablets. Now contains hesperidin complex.*

## BANAUSEA

TABLETS

ANTINAUSEANT, ANTIEMETIC — BAN NAUSEA AND VOMITING OF PREGNANCY  
. . . SAFELY . . . EFFECTIVELY . . . ECONOMICALLY.

*Just prescribe BANAUSEA tablets, one upon arising and one at bedtime. Turn your patients' blue mornings pink with BANAUSEA tablets.*

*Samples upon request.*

*Reference: I. Peña, E. F., Med. Times, 82-921, 1954.*



Amfre-Grant, Inc., Brooklyn 26, N. Y.



*for laxative results without laxative harshness*

**in** **DOXIDAN<sup>®</sup>** **THE SURFACTANT LAXATIVE**  
**obstetrics**

"We consider Doxidan to be superior to the agents we have previously employed in the treatment of constipation in postpartum patients. Not only was it more effective, but also its use was associated with almost complete freedom from side effects . . . flatulence, cramping and 'griping' were notably absent . . . 'rebound constipation' and the danger of subsequent habit formation are largely obviated by the use of this logical combination of a potent fecal softener with a mild peristaltic stimulant."<sup>1</sup>

**DOSAGE AND SUPPLY:** One or two capsules administered at bedtime for two or three days or until bowel movements are normal. Each maroon Doxidan capsule contains 50 mg. Danthron (1,8-dihydroxyanthraquinone) and 60 mg. calcium bis-(dioctyl sulfosuccinate). Bottles of 30 and 100 soft gelatin capsules.

1. Bell, A.: Management of Constipation in the Puerperium. Accepted N. Y. S. J. Med.



**LLOYD BROTHERS, INC.**

CINCINNATI 3, OHIO, U.S.A.





she can choose her own silver...

but she needs **your** help in planning her family

**Delfen**<sup>®</sup>  
VAGINAL CREAM

THE MODERN CHEMICAL SPERMICIDE

**Preceptin**<sup>®</sup>  
VAGINAL GEL

THE SPERMICIDAL GEL WITH BUILT-IN BARRIER

PRESCRIBED WITH CONFIDENCE FOR SIMPLE, EFFECTIVE CONTRACEPTION

00559

# CONVENIENT SINGLE-USE TUBES



## 'LUBAFAX'

brand

### SURGICAL LUBRICANT

#### 5 GRAM TUBE FEATURES

##### STERILITY—

Minimizes cross-contamination

##### CONVENIENCE—

Snap off the tip and it's ready to use

##### ECONOMY—

Low unit cost of single-use tube may be added to patient's charge.



*Also Available*  
2 oz. and 5 oz. Tubes

- Sterile
- Transparent
- Nonirritating
- Adheres firmly to instruments
- Washes off easily
- No unpleasant odor
- Suitable viscosity for optimum lubrication



BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, N. Y.

**New  
Hygroton®**

brand of chlorthalidone

**Geigy**

**longest in action...  
smoothest in effect**

**in hypertension  
and edema**

greater loss of sodium  
lesser loss of potassium

A new antihypertensive-saluretic,  
Hygroton, now enables still more effective  
control of hypertension and edema.

**more evenly sustained therapeutic response**

Because it is more prolonged in action  
than any other diuretic,<sup>1</sup> Hygroton affords  
a smoother, more evenly sustained  
response.

**more nearly pure natriuretic effect**

Hygroton produces only minimal  
potassium loss . . . affords a better sodium-  
potassium ratio than other saluretics.<sup>3</sup>

**more liberal diet for the patient**

As a rule, with Hygroton, restriction of  
dietary salt is unnecessary.

**more convenience and economy**

For maintenance therapy three doses per  
week suffice to manage the vast majority  
of cases.<sup>2</sup>

**In arterial hypertension**

Sustained control without side reactions.

**In edematous states**

Copious diuresis without electrolyte  
imbalance.

Hygroton®, brand of chlorthalidone: White,  
single-scored tablets of 100 mg. in bottles of 100.

**References:**

(1) Stenger, E. G., et al.: Schweiz. med. Wchnschr.  
89:1126, 1959. (2) Fuchs, M., Res: et al.: Current  
Therap. Research 2:11, January, 1960. (3)  
Ford, R. V.: Manuscript submitted for publication.



Geigy, Ardsley, New York

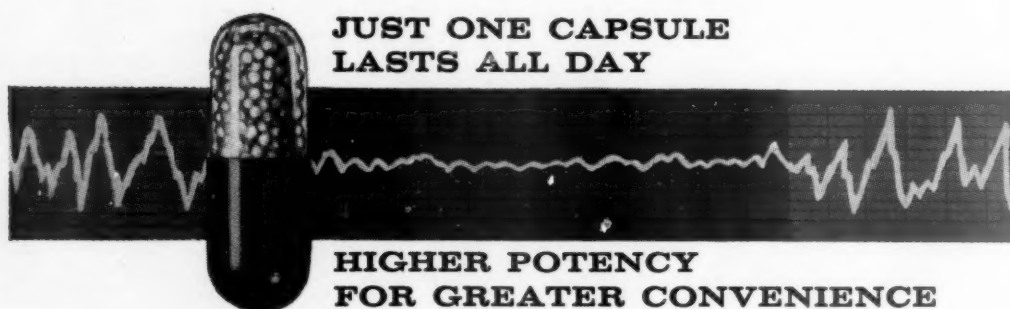
HY 234-60

**NEW AND EXCLUSIVE**

**FOR SUSTAINED  
TRANQUILIZATION**

MILTOWN® (*meprobamate*) now available  
in 400 mg. continuous release capsules as

**Meprospan®-400**



**JUST ONE CAPSULE  
LASTS ALL DAY**

**HIGHER POTENCY  
FOR GREATER CONVENIENCE**

- relieves *both* mental and muscular tension without causing depression
- does not impair mental efficiency, motor control, or normal behavior

**Usual dosage:** One capsule at breakfast,  
one capsule with evening meal

**Available:** *Meprospan-400*, each blue capsule contains  
400 mg. Miltown (*meprobamate*)  
*Meprospan-200*, each yellow capsule contains  
200 mg. Miltown (*meprobamate*)  
*Both potencies in bottles of 30.*

**W** WALLACE LABORATORIES, *New Brunswick, N. J.*

CHE-8427



*to control their "heartburn"...*



Prescribe GELUSIL antacid for  
fast, prolonged relief. All antacid  
in action—nonconstipating—  
contains no laxative

*pleasant-tasting*

**GELUSIL®**

GE-0803

*the physician's antacid*





# FOR EASIER ELIMINATION IN OBSTETRICS OR SURGERY



## TARGET ACTION

*specifically on the large bowel*

### **DORBANE®**

(1, 8-dihydroxyanthraquinone)

selective peristaltic stimulant • smooth, overnight action  
• no griping • well tolerated • non-habituating  
Available in 75 mg. scored tablets and suspension.

WHERE STOOL SOFTENING IS ALSO INDICATED

### **DORBANTYL® FORTE**

(Dorbane, 50 mg. + dioctyl sodium sulfosuccinate, 100 mg.)\*

Double-strength capsules for maximum economy and convenience.

### **DORBANTYL®**

(Dorbane, 25 mg. + dioctyl sodium sulfosuccinate, 50 mg.)\*

For lower dosage and in children.  
Available in capsules and suspension.

\*In proportions proved optimal by clinical trial in over 550 cases.  
(Marin, M. M.: Clin. Med. 4:151, 1967.)



SCHENLABS PHARMACEUTICALS, INC. • NEW YORK 1, N. Y. Manufacturers of NEUTRAPEN® for penicillin reactions.

by every  
standard  
the drug for  
"morning sickness"

**Bonine**<sup>®</sup>

brand of metizine hydrochloride



#### IN BRIEF

BONINE is an antiemetic which provides rapid and prolonged protection against nausea and vomiting due to a variety of causes. A single dose of BONINE is usually effective for 24 hours. Thus, BONINE can be taken at bedtime to help prevent "next morning" sickness.

**INDICATIONS:** Valuable in the symptomatic relief of nausea and vomiting of pregnancy. Also indicated for motion sickness, radiation sickness, vertigo associated with Ménière's syndrome, labyrinthitis, fenestration procedures, vestibular dysfunction, and dizziness associated with cerebral arteriosclerosis.

**ADMINISTRATION AND DOSAGE:** For control of nausea and vomiting of pregnancy, a daily dose of 25 to 50 mg. is usually effective. For dosage schedules in other indications, see package insert.

**SIDE EFFECTS:** Not a phenothiazine, the side effects reported in association with Bonine have been mild and/or transient and consist of occasional drowsiness, dryness of the mouth, and blurred vision. Drowsiness is seen less frequently with BONINE in therapeutic dosages than with most other effective antiemetics.

**PRECAUTIONS:** As with other antihistaminic compounds, the physician should inform patients of the need for caution in driving a car or when engaged in other activities requiring alertness. There are no known contraindications to BONINE.

**SUPPLIED:** BONINE Tablets, scored, tasteless, 25 mg. BONINE Chewing Tablets, mint-flavored, 25 mg. BONINE Elixir, cherry-flavored, 12.5 mg. per teaspoonful (5 cc.).

More detailed professional information available on request.



# RONCOVITE®-MF IS RAPIDLY BECOMING THE DRUG OF CHOICE IN ANTI-ANEMIA THERAPY...

because...

Cobalt is the only clinically proved therapeutic agent which enhances the formation of erythropoietin, the hormone which regulates erythropoiesis in the body.<sup>1-3</sup>

because...

Roncovite through the effect of Cobalt-enhanced erythropoietin improves iron utilization by activating this normal physiologic process.<sup>3-4</sup>

because...

The result is a more rapid and complete hematologic response in the anemic patient...<sup>5-9</sup>

and because...

The safety of Roncovite has been thoroughly attested in published literature and demonstrated during the administration of over 365 million doses.<sup>6,10,11</sup>

1. Goldwasser, E.; Jacobson, L. O.; Fried, W., and Pizak, L. F.: *Blood* 13:55 (Jan.) 1958. 2. Murdock, H. R. Jr.: *Am. Pharm. Assoc. (Sci. Ed.)* 48:140, 1959. 3. Goldwasser, E.; Jacobson, L. O.; Fried, W., and Pizak, L.: *Science* 125:1085 (May 31) 1957. 4. Center, W. M.: *Clin. Med.* 7:713 (April) 1960. 5. Holly, R. G.: *Obst. & Gynec.* 9:299 (Mar.) 1957. 6. Ausman, D. O.: *Journal-Lancet* 76:290 (Oct.) 1956. 7. Flynn, R. T.: *Therapy with Cobalt and Iron for Correction of Anemia in Pregnancy*, Presented at Michigan and Wayne Co. Acad. GP, Postgrad. Clinic, Detroit, Mich., Nov. 11-12, 1959. 8. Tevetoglu, F., and Ozkaragos, K.: *M. Times* 86:81 (Jan.) 1958. 9. Craig, P. E.: *Clin. Med.* 6:597 (April) 1959. 10. Hill, J. M.; LaJous, J., and Sebastian, F. J.: *Cobalt Therapy in Anemia*, *Texas J. Med.* 51:686 (Oct.) 1955. 11. Tevetoglu, F.: *J. Pediat.* 49:46 (July) 1956.

Please write for monograph,  
"The Hormone Erythropoietin."  
Roncovite literature also  
available on request.

**LLOYD BROTHERS, INC.**

#### EACH ENTERIC COATED, GREEN TABLET CONTAINS:

Cobalt chloride . . . . . 15 mg.  
(Cobalt as Co. 3.7 mg.)

Ferrous sulfate, exsiccated . . . . . 100 mg.

**DOSAGE:** The maximum adult dose of Roncovite-MF is one tablet after each meal and at bedtime.

CINCINNATI 3, OHIO



Photos Courtesy F. C. Gindhart, M.D.

## For more successful pregnancies in habitual aborters

When added to your individualized anti-abortion regimen, NUGESTORAL may help you bring more habitual aborters to successful term.

By supplying five therapeutic agents known to contribute to fetal salvage, NUGESTORAL creates an optimal maternal environment for the maintenance of pregnancy.

*Nugestoral* supplies in each daily dose of three tablets:

Progestoral® (Ethisterone) .....	45.0 mg.
<ul style="list-style-type: none"> <li>• Progestational action helps maintain fetus</li> <li>• Relieves uterine spasticity</li> </ul>	
Ascorbic Acid (Vitamin C) .....	525.0 mg.
Purified Hesperidin .....	487.5 mg.
(equiv. 600 mg. hesperidin complex)	
<ul style="list-style-type: none"> <li>• Prevent or correct abnormal capillary fragility</li> <li>• Protect and strengthen decidual vessels</li> </ul>	
Menadione Sodium Bisulfite .....	6.0 mg.
(U.S.P. Equivalency)	
<ul style="list-style-type: none"> <li>• Prevents hypoprothrombinemia in mother and child</li> </ul>	
dl, Alpha-Tocopherol Acetate (Vitamin E) .....	10.5 mg.
<ul style="list-style-type: none"> <li>• Extra nutritional insurance</li> </ul>	

**DOSAGE:** *Prophylactic* — One NUGESTORAL tablet t.i.d. from diagnosis through at least the second trimester.

*Symptomatic* — Two tablets t.i.d. or q.i.d. until symptoms are controlled. Then one tablet t.i.d.

Available in boxes of 30 and 100. Write for copies of recent clinical reports.



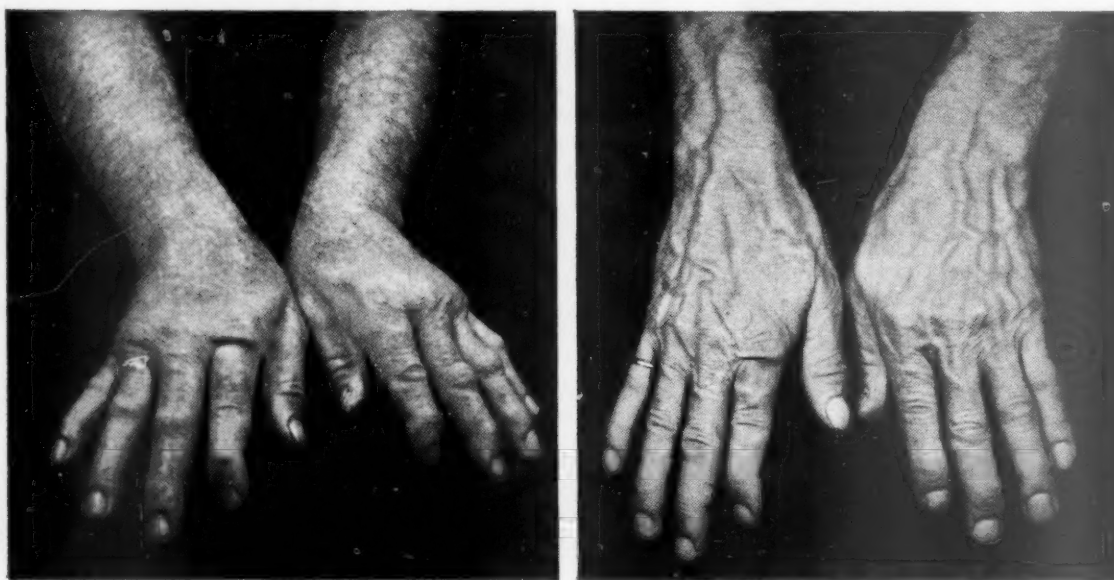
ORGANON INC., ORANGE, N. J.

# Nugestoral®

RATIONAL THERAPY  
IN A WIDE RANGE OF  
COMMON SKIN DISORDERS

# NEW FURACIN<sup>®</sup>-HC (NITROFURAZONE 0.2% AND HYDROCORTISONE 1%, EATON) CREAM

INFECTED AND POTENTIALLY INFECTED DERMATOSES / PYODERMAS / ULCERS  
BURNS / AFTER PLASTIC, ANORECTAL AND MINOR SURGERY



FURACIN-HC Cream combines the anti-inflammatory and antipruritic effect of hydrocortisone with the dependable antibacterial action of FURACIN<sup>®</sup>, brand of nitrofurazone—the most widely prescribed single topical antibacterial. The broad bactericidal range of FURACIN includes stubborn staphylococcal strains, and there has been no development of significant bacterial resistance after more than a dozen years of widespread clinical use. FURACIN is gentle to tissues, does not retard healing; its low sensitization rate is further minimized by the presence of hydrocortisone.

FURACIN-HC Cream is available in tubes of 5 Gm. and 20 Gm. Fine vanishing cream base, water-soluble.

NITROFURANS—a unique class of antimicrobials / EATON LABORATORIES, NORWICH, NEW YORK  
Products of Eaton Research





BUFFERED TO MAINTAIN A NORMAL, LOW pH...LOW SURFACE TENSION  
FOR THOROUGH CLEANSING OF THE VAGINAL MUCOSA...

Buffers in Massengill Powder solution (pH 3.5 - 4.5) inhibit the neutralizing effect of an alkaline mucosa, maintaining a healthy, low pH for 4 to 6 hours in ambulant patients and up to 24 hours in recumbent patients. This low pH represses the propagation of candida, trichomonas vaginalis, and pathogenic bacteria but permits growth of the beneficial Döderlein bacillus. In contrast, an ordinary, unbuffered douche like vinegar is neutralized within 30 minutes after application. ● Low surface tension of Massengill Powder solution (50 dynes/cm.) enables it to penetrate and cleanse all the folds of the vaginal mucosa more effectively than vinegar (surface tension of 72 dynes/cm.). It also makes cell walls of infecting organisms more susceptible to therapy.

# MASSENGILL<sup>®</sup> POWDER

*the buffered acid vaginal douche with low surface tension*

THE S. E. MASSENGILL COMPANY Bristol, Tennessee • New York • Kansas City • San Francisco



PATIENTS PREFER

# MASSENGILL<sup>®</sup> POWDER

*the buffered acid vaginal douche with low surface tension*

Massengill Powder soothes inflamed tissues, deodorizes, and tends to diminish excessive vaginal secretions. Patients like its clean, refreshing odor.

Massengill Powder is indicated for routine feminine hygiene to guard against infection, and as an adjunct in the management of candida, trichomonas, staphylococcus, and streptococcus vaginal infections.

Contains: Ammonium Alum, Boric Acid, Phenol, Menthol, Berberine, Thymol, Eucalyptol, and Methyl Salicylate. *Write for samples and detailed literature.*

THE S. E. **M**ASSENGILL COMPANY

Bristol, Tennessee • New York • Kansas City • San Francisco

# explodes trichomonads

## VAGISEC®

LIQUID AND JELLY

**93.1% "cure" rate using  
strictest criterion—  
negative cultures for  
3 consecutive months**



before VAGISEC



30 days' "cure"

**Repeated negative cultures**, following treatment with VAGISEC liquid and jelly, confirmed "cures" in 93.1% of trichomoniasis patients (54 of 58) treated by Giorlando and Brandt.<sup>1</sup> These patients were followed up, using cultures, for a minimum of three months, many for as long as eight months. *All* remained negative. Using the same strict criterion of negative cultures, Weiner achieved comparable success<sup>2</sup>—46 of 51 patients freed of trichomonads.

VAGISEC therapy is consistently characterized by immediate relief of painful symptoms—few recurrences.

**To help rule out conjugal re-infection**—Husbands willingly cooperate as a part of the wife's treatment when RAMSES,<sup>®</sup> the pure gum rubber prophylactics with "built-in" sensitivity, are suggested for use routinely.

Active ingredients in VAGISEC liquid: Polyoxyethylene nonyl phenol; Sodium ethylene diamine tetra-acetate; Sodium dioctyl sulfosuccinate. In addition, VAGISEC jelly contains Alcohol 5% by weight.

1. Giorlando, S. W., and Brandt, M. L.: *Am. J. Obst. & Gynec.* 76:666 (Sept.) 1958. 2. Weiner, H. H.: *Clin. Med.* 5:25 (Jan.) 1958.

VAGISEC and RAMSES are registered trade-marks of Julius Schmid, Inc.

**JULIUS SCHMID, INC.**  
423 West 55th Street, New York 19, N. Y.



**in premenstrual  
tension  
clinicians report  
rapid relief with**



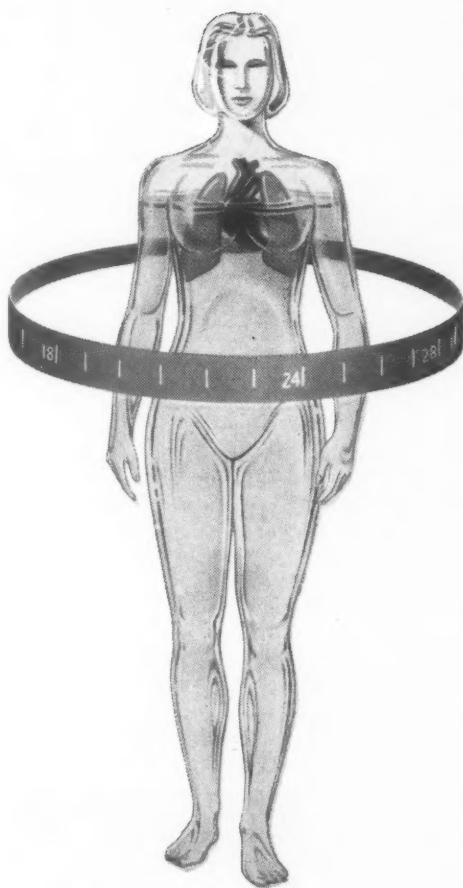
**HYDRODIURIL<sup>®</sup>**

HYDROCHLOROTHIAZIDE

**increased potency—without corresponding increase in side effects**

*Fuchs, M. and Moyer, J.:  
Diseases of the Chest 35:314, (March) 1959.*

“Premenstrual edema is present in 40% of women and...consists of weight gain, subcutaneous edema, emotional lability, breast turgidity, anxiety and tension.” In addition to controlling the objective symptoms of premenstrual tension, HYDRODIURIL may afford relief of subjective complaints including tension, nervousness and headache.



**DOSAGE:** 25 to 50 mg. of HYDRODIURIL once or twice a day, beginning the first morning of symptoms and continuing until the onset of the menses.

**SUPPLIED:** 25 and 50 mg. scored tablets HYDRODIURIL (hydrochlorothiazide) in bottles of 100 and 1,000.

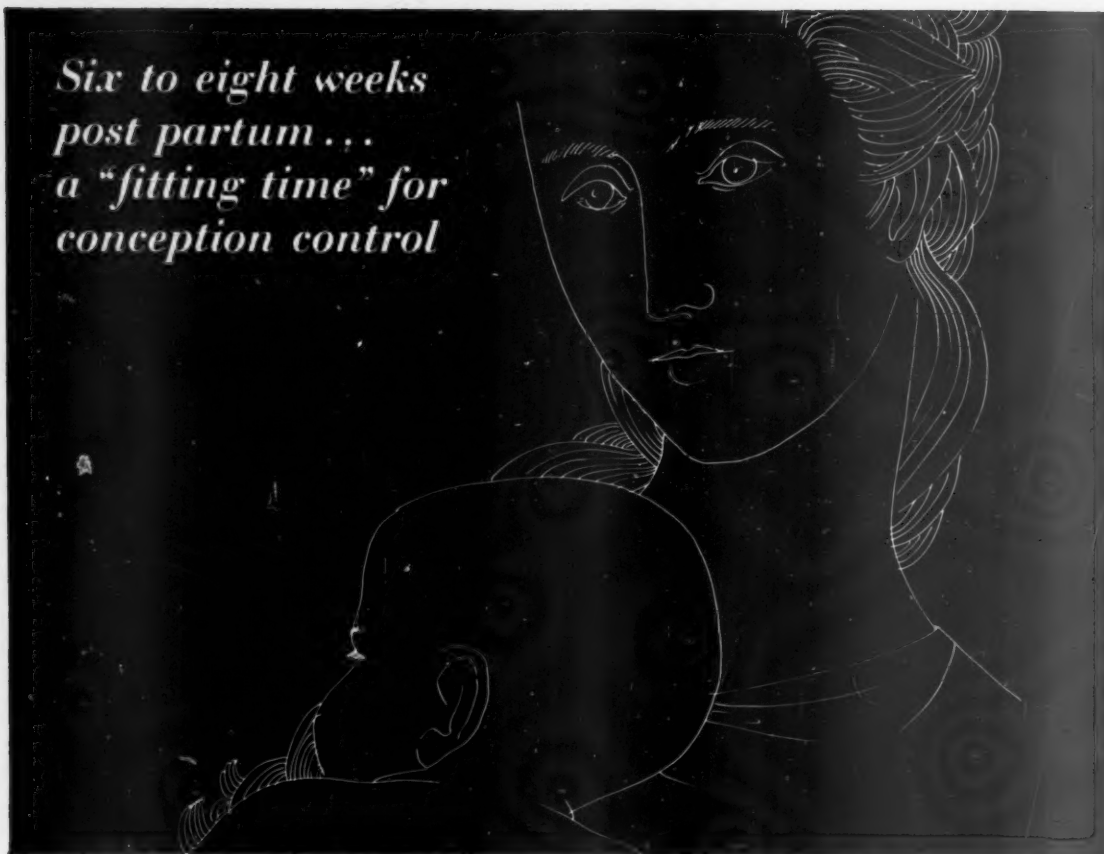
HYDRODIURIL is a trademark of Merck & Co., Inc.

Additional information on HYDRODIURIL is available to the physician on request.



**MERCK SHARP & DOHME**  
Division of Merck & Co., Inc. West Point, Pa.

*Six to eight weeks  
post partum...  
a "fitting time" for  
conception control*



Conception control becomes a matter of special concern six to eight weeks post partum, when the new mother looks to you for advice on the best way to plan the balance of her family. Reliable conception control can be virtually assured with the diaphragm and jelly method, at least 98 per cent effective.<sup>1</sup>

*Now—cushioned comfort  
... two ways*

Your patient experiences special physical comfort when you prescribe either the standard RAMSES® Diaphragm or the new RAMSES BENDEX®, an arc-ing type diaphragm.

The regular RAMSES Diaphragm, suitable for most women, is made of pure gum rubber, with a dome that is unusually light and velvet smooth. The rim, encased in soft rubber, is flexible in all planes permitting complete freedom of motion. For those women who prefer or require an arc-ing type diaphragm, the new RAMSES BENDEX embodies all of the superior features of the conventional RAMSES Diaphragm, *together with the very best hinge mechanism contained in any arc-ing diaphragm.* It thus affords lateral flexibility to supply the proper degree of spring tension without discomfort.

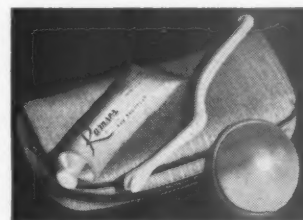
RAMSES, BENDEX, and "TUK-A-WAY" are registered trademarks of Julius Schmid, Inc.

\*Active agent, dodecaethyleneglycol monolaurate 5%, in a base of long-lasting barrier effectiveness.

*For added protection—RAMSES  
"10-Hour" Vaginal Jelly\**

RAMSES Jelly is uniquely suited for use with either type of RAMSES Diaphragm. It is by design not static, but flows freely over the rim and surface of the diaphragm to add lubrication and to form a spermtight seal over the cervix, which is maintained for *ten full hours* after insertion. It is nonirritating and nontoxic.

You can now prescribe a complete unit for either type of diaphragm. RAMSES "TUK-A-WAY"® Kit #701 contains the regular RAMSES Diaphragm with introducer and a 3-ounce tube of RAMSES Jelly; RAMSES "TUK-A-WAY" Kit #703 contains the RAMSES BENDEX Diaphragm and Jelly tube. Each kit is supplied in an attractive plastic zippered case, beautifully finished inside and out. Both types are now available at key prescription pharmacies.

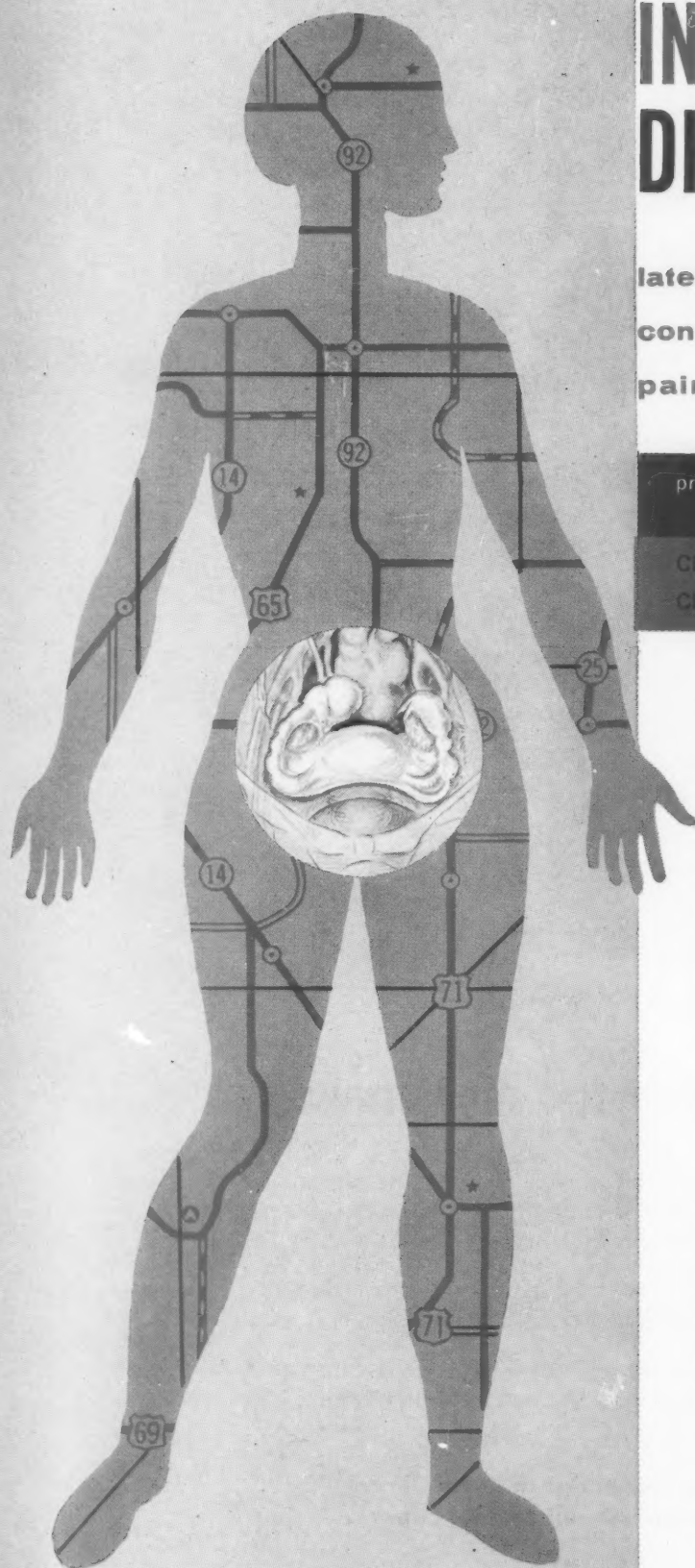


Reference: 1. Tietze, C.: Proceedings, Third International Conference Planned Parenthood, 1953.

*Ramses®* Diaphragms  
and Jelly

**JULIUS SCHMID, INC.** 423 West 55th Street, New York 19, N. Y.





# PELVIC INFLAMMATORY DISEASE?

latest clinical data show Chymar controlled inflammation, swelling and pain in 9 out of every 10 patients.<sup>1,2</sup>

preparation	no. of patients	improved	not improved
Chymar Aqueous <sup>1</sup>	219	187 (85%)	32 (15%)
Chymar Buccal <sup>2</sup>	99	88 (90%)	11 (10%)

"Of the group (15%) which did not respond to treatment, most had advanced pelvic masses which also had failed to respond to other conventional therapy used previously."<sup>1</sup>

1. Reich, W. J., and Nechtow, M. J.: *Am. Pract. & Digest Treat.* 11:45, 1960. 2. Reich, W. J., and Nechtow, M. J.: *Scientific Exhibit*, Chicago Med. Soc. (March) 1960.

SYSTEMIC ROUTE TO FASTER HEALING

## CHYMAR<sup>®</sup>

*Buccal / Aqueous / Oil*  
the superior anti-inflammatory enzyme

CONTROLS INFLAMMATION, SWELLING AND PAIN

### CHYMAR Buccal

Crystallized chymotrypsin in a tablet formulated for buccal absorption. Bottles of 24 tablets. Enzymatic activity, 10,000 Armour Units per tablet.

### CHYMAR Aqueous

Solution of crystallized chymotrypsin in sodium chloride injection for intramuscular use. Vials of 5 cc. Enzymatic activity, 5000 Armour Units per cc.

### CHYMAR

Suspension of crystallized chymotrypsin in oil for intramuscular injection. Vials of 5 cc. Enzymatic activity, 5000 Armour Units per cc.

ARMOUR PHARMACEUTICAL COMPANY • KANKAKEE, ILLINOIS

*Armour Means Protection*





**NIAMID<sup>®</sup>**

brand of nialamide

the mood brightener

## ...brightens dark days of the menopause

NIAMID has had excellent results during the menopause — easing difficult mental adjustment caused or complicated by depression. As the patient's attitude improves, she often takes more interest in her appearance and becomes more sociable.

NIAMID acts gradually, gently, without rapid jarring of physical or mental processes. The patient's family usually is first to notice her reawakening interest in life.

Although NIAMID has proved to be an unusually well tolerated antidepressant, the possibility of hepatic reactions should be kept in mind, especially where there is a history of liver disease.

**More than 500,000 prescriptions in many clinical conditions — more than 90 published papers.**

Supplied as 25 and 100 mg. scored tablets. Professional Information Booklet available on request from the Medical Department, Pfizer Laboratories, Brooklyn 6, N. Y.

**Pfizer** Science for the world's well-being™



## obstetrical sedation without depressing vital functions of mother or infant

**labor—early stages:** PHENERGAN provides psychic sedation, relieves apprehension, permits elimination of barbiturates, and produces light sleep. It reduces narcotic and analgesic requirements; prevents and controls nausea and vomiting.

**labor—definitely established:** PHENERGAN facilitates induction of anesthesia, permits reduction in analgesic requirements, and controls nausea and vomiting. It provides sedation and a restful postpartum period.

For further information on prescribing and administering PHENERGAN see descriptive literature, available on request.

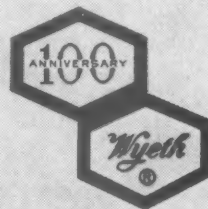
INJECTION • TABLETS • SYRUP • SUPPOSITORIES

# PHENERGAN<sup>®</sup>

HYDROCHLORIDE

*Promethazine Hydrochloride, Wyeth*

Wyeth Laboratories Philadelphia 1, Pa.



A Century of  
Service to Medicine





# Tigan

NEW 250 mg CAPSULES

*to stop as well as prevent  
nausea and vomiting of pregnancy*

Safe and  
Sound  
in any  
pregnancy

*for a pregnancy unmarred by "morning sickness,"  
uncomplicated by hyperemesis gravidarum*

TIGAN is equal in effectiveness to the most potent antiemetics. It not only safely prevents "morning sickness," but usually stops even severe, intractable vomiting.<sup>1</sup>

**Acts at the CTZ—like the most potent antiemetics**

Tigan blocks emetic impulses at the chemoreceptor trigger zone (CTZ),<sup>2</sup> a medullary structure which activates the vomiting center. To this extent, Tigan is like the most potent antiemetic agents—the phenothiazines.<sup>3</sup>

**Safe—without the side effects of the antihistamines**

In extensive clinical studies,<sup>1,4,6</sup> Tigan has demonstrated a virtually complete absence of side effects. It has no sedative properties;<sup>4,6</sup> therefore, patients receiving Tigan may drive an automobile without the hazard of drowsiness, and carry on their household activities without being troubled by added lethargy or sleepiness.

**Safe—without the risks of the phenothiazines**

The mode of antiemetic action is the only similarity between Tigan and the phenothiazines. Chemically and pharmacologically, they are completely unrelated.<sup>2</sup> Tigan has no tranquilizing properties, hypotensive action, supramedullary effects, extrapyramidal tract stimulation or hepatic toxicity.<sup>1,4,6</sup> In laboratory findings there has been *not one reported instance of abnormality due to Tigan*.<sup>1,4,6</sup>

**No known contraindications**

There are no known contraindications, no special precautions to complicate Tigan therapy.

# Tigan

NEW 250 mg CAPSULES

*no known contraindications...no sedative properties...no tranquilizer side effects*

**Usual Dosage:**

*In nausea and vomiting of pregnancy, one 250-mg capsule at bedtime and equivalent doses immediately upon awakening and throughout the day as necessary, up to a total of four doses per day.*

**How Supplied:**

TIGAN CAPSULES, 250 mg, blue—bottles of 50; 100 mg, blue and white—bottles of 100 and 500.

TIGAN MULTIDOSE VIALS, 20 cc (100 mg/cc)—boxes of 1.

TIGAN AMPULS, 2 cc (100 mg/cc)—boxes of 6 and 25.

TIGAN SUPPOSITORIES, 200 mg each—boxes of 6.

**References:**

1. Reports on file, Roche Laboratories.
2. W. Schallek, G. A. Heise, E. F. Keith and R. E. Bagdon, *J. Pharmacol. & Exper. Therap.*, 126:270, 1959.
3. L. S. Goodman and A. Gilman, *The Pharmacological Basis of Therapeutics*, ed. 2, New York, The Macmillan Company, 1956, p. 1066.
4. O. Brandman, *Gastroenterology*, 38:777, 1960.
5. I. Roseff, W. B. Abrams, J. Kaufman, L. Goldman and A. Bernstein, *J. Newark Beth Israel Hosp.* 9:189, 1958.
6. W. B. Abrams, I. Roseff, J. Kaufman, L. M. Goldman and A. Bernstein, *New York J. Med.*, 59:4217, 1959.

ROCHE LABORATORIES



Division of Hoffmann-La Roche Inc.  
Nutley 10, N. J.

TIGAN® Hydrochloride—4-(2-dimethylaminoethoxy)-N-(3,4,5-trimethoxybenzoyl) benzylamine hydrochloride

*Enthusiastically Received...*

# CLINICAL PHARMACOLOGY

The first issue, published in January, proved C. P. T. an immediate success! Here are just a few appraisals from scores of letters of appreciation received from subscribers.

*"C. P. T. has pleased me greatly . . . I feel that every practitioner in medicine is in need of such a publication."*

*"The Current Drug Therapy article on the phenothiazines was, to me, very instructive. It dispelled some of the fog in which I found myself in regard to tranquilizers."*

*"Here was a journal I had been waiting for."*

*"It should rise as the major guide for the use of newer therapeutic agents."*

*"Especially interested in Harrell's excellent review." (Fungus diseases)*

*"Particularly did I like the articles on the anthelmintics and the phenothiazines."*

*"Undoubtedly acceptance by people with a primary interest in drugs will be immediate and widespread."*

*"Informative and concise, not only supplying me with new information but also helping me arrange the information in my mind for easier recall."*

*"Excellent . . . high standards and wide range of articles . . . most welcome!"*

*"If January issue is an example of future issues, you can place me on the list of permanent subscribers."*

## **Purpose and Scope of C.P.T.**

C. P. T. has been established to gather together and publish in one place the best available papers on clinical pharmacology and therapeutics. Contents are presented with the needs of busy clinicians in mind; original papers are concise; reviews and symposia are comprehensive; all material is authoritative. It is edited particularly for clinicians—for family physicians, internists, pediatricians, dermatologists, surgeons, anesthesiologists and others who always must have the latest dependable pharmacological information at hand. Its scope is limited to the effects of drugs in man.

**A BIMONTHLY PUBLICATION**



FROM THE VERY FIRST ISSUE!

# and THERAPEUTICS

Official Publication of the  
AMERICAN THERAPEUTIC SOCIETY

Editor  
WALTER MODELL, M.D.

## Editorial Board

W. A. Bain, M.D., Director, Smith Kline & French  
Research Institute

Edward A. Carr, Jr., M.D. Associate Professor of  
Pharmacology

Windsor Cutting, M.D. Professor of Experimental  
Therapeutics

Athur C. DeGraff, M.D. Professor of Therapeutics

James M. Dille, M.D. Professor of Pharmacology

Alan K. Done, M.D. Assistant Professor of Pediatrics

Dale G. Friend, M.D. Assistant Professor of Medicine

George E. Griffith, M.D. Professor of Medicine

Arthur Grollman, M.D. Professor of Experimental  
Medicine

Harriet Hardy, M.D. Associate Professor of Medicine

Raymond W. Houde, M.D. Associate, Sloan-Kettering  
Institute for Cancer

Ernest Jawetz, M.D., Ph.D. Professor of Microbiology

David A. Karnofsky, M.D. Member, Sloan-Kettering  
Institute for Cancer

Kenneth G. Kohlstaedt, M.D. Director, Clinical  
Research Division, Eli Lilly and Company

Herbert S. Kupperman, Ph.D., M.D. Associate  
Professor of Medicine

D. R. Laurence, M.D. Lecturer in Applied  
Pharmacology and Therapeutics

T. A. Loomis, M.D., Ph.D. Professor of Pharmacology

Donald Mainland, M.B., D.Sc. Professor of  
Medical Statistics

H. Houston Merritt, M.D. Professor of Neurology,  
Dean of the Faculty of Medicine

Eric Nilsson, M.D. Head, Department of Anesthetics

Carl C. Pfeiffer, Ph.D., M.D. Professor of  
Pharmacology

William B. Rawls, M.D. Attending Physician,  
St. Clair Hospital

Marion B. Sulzberger, M.D. Professor and  
Chairman, Department of Dermatology

Leroy D. Vandam, M.D. Clinical Professor of  
Anesthesia

Walton Van Winkle, Jr., M.D. Vice-President,  
Research, Ethicon, Inc.

Andrew Wilson, M.D. Professor of Pharmacology and  
General Therapeutics

Gerhard Werner, M.D. Associate Professor of  
Pharmacology

## TYPICAL PAPERS

### In the January-February Issue:

The Phenothiazines. *Dale G. Friend*

Modern Treatment of The Systemic  
Fungus Diseases. *E. R. Harrell*

Man's Hand In Bacterial Resistance.  
*Ernest Jawetz*

Newer Drugs in Amebiasis. *Hamilton  
H. Anderson*

The Actions And Uses of Anthel-  
mintics. *H. W. Brown*

### In the March-April Issue:

Modern Diuretics And Diuretic  
Therapy. *Dale G. Friend*

The Nature of The Antirheumatic  
Action of Salicylates. *A. K. Done*

Nitrofurantoin (Furadantin) In The  
Biliary Tract. *I. A. Feder, et al*

Developing And Testing of New Drugs  
By The Pharmaceutical Industry.  
*Kenneth G. Kohlstaedt*

Orally Active Hypoglycemic Sub-  
stances And The Rationale of Their  
Use. *R. Levine*

### To Appear in Early Issues:

Mechanism of The Antihypertensive  
Effects of Diuretics. *E. D. Freis*

The Sensitivity And Validity of Drug  
Evaluations in Man. *W. Modell*

Current Uses of Iodides In Therapy.  
*William F. Kremer*

Abnormal Symptoms, Signs and Labo-  
ratory Tests During Treatment  
With Phenothiazine Derivatives.  
*Leo E. Hollister, et al*

The Pharmacology of Neuromuscular  
Blocking Agents In Man. *F. F.  
Foldes*

## Enroll Now

### USE THIS COUPON!

Subscribe to this timely publi-  
cation devoted exclusively to  
clinical pharmacology and thera-  
peutics! Take advantage of the  
generous introductory offer de-  
scribed on the enrollment form!

THE C. V. MOSBY COMPANY, 3207 Washington Boulevard, St. Louis 3, Missouri

Dear Sirs:

Date.....

Enroll me as a Subscriber to CLINICAL PHARMACOLOGY AND THERAPEU-  
TICS. Send the first two issues free. Bill me for \$12.50 (Canada & Latin  
America, \$13.00; elsewhere, \$13.50) for the next six bimonthly issues.

☐ I'm enclosing my check for \$..... ☐ Bill me,  
(Attach your check; receive 3 issues free!)

☐ I am in Gen. Practice ☐ I specialize (☐ full-time ☐ part-time) in:

Dr.....

Address.....

City.....Zone.....State.....



multiparas need more...

# NATALINS<sup>®</sup> COMPREHENSIVE

Vitamins and minerals

tablets

give them more...more iron, more calcium and more vitamin C

Natalins Comprehensive tablets are formulated to meet the special vitamin-mineral needs of the multipara, whose nutritional stores may have been depleted by successive pregnancies.

Obviously, they are ample for the primigravida

as well. Supplying generous amounts of *iron* (40 mg.), *calcium* (250 mg.), and *ascorbic acid* (100 mg.), each Natalins Comprehensive tablet also provides significant quantities of nine other important vitamins and minerals. Recommended dosage is only one tablet daily.

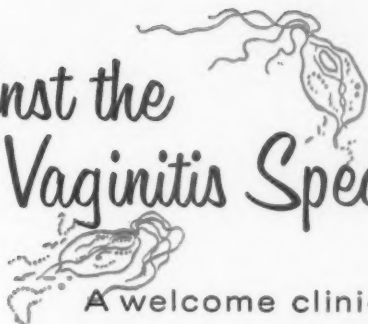


Mead Johnson

Symbol of service in medicine

GENCO

# Against the "Vaginitis Spectrum"

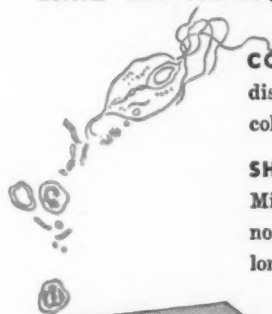


TRICHOMONAS  
MONILIA  
BACTERIA

A welcome clinical advance...  
effective medication  
in an appealing form

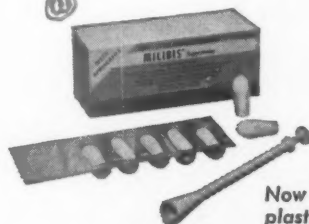


Soft and pliant as a tampon, the Milibis vaginal suppository offers proved therapeutic action\* in a vehicle giving unusual clinical advantages to both patients and physician.



**COVERS CERVIX AND VAGINAL WALL**—The pliant Milibis suppository disintegrates readily and molds itself to the cervix as well as the columns and rugae of the vaginal vault.

**SHORT DOSAGE SCHEDULE**—The short course of treatment with Milibis—only 10 suppositories in most cases—together with the clean, odorless, non-staining qualities eliminates psychic barriers which often interrupt longer treatments before complete cure.



SUPPLIED: BOXES OF 10  
with applicator.

Now supplied with  
plastic applicator

- SANITARY
- INSURES CORRECT  
SUPPOSITORY PLACEMENT

## MILIBIS® Vaginal Suppositories

Winthrop LABORATORIES  
New York 18, N. Y.

\*97 per cent effective in a study of 564 cases;  
94 per cent effective in a series of 510 cases.

Milibis (brand of glycobarsol), trademark reg. U. S. Pat. Off.





Each tablet contains:

Provera (medroxyprogesterone acetate) 2.5 mg.  
 Cardrase (ethoxzolamide) ..... 35 mg.  
 Levanil (ectylurea) ..... 300 mg.

DOSAGE: 1 tablet 1 or 2 times daily, 5-10 days  
 before the period.

THE UPJOHN COMPANY / KALAMAZOO, MICHIGAN

# CYTRAN<sup>\*</sup>

## GETS AT THE CAUSE

to restore hormonal balance...

*corrective therapy* Because Cytran contains the new progestin, Provera,<sup>†</sup> you can now reach the *cause* of premenstrual tension—hormonal imbalance. Estrogen-progesterone ratio is adjusted to more normal premenstrual balance. Thus even abdominal discomfort, shakiness, fatigue—symptoms incompletely controlled by mere symptomatic treatments—are effectively relieved.

to comfort the patient...

*symptomatic therapy* An effective diuretic (Cardrase<sup>†</sup>) and a mild tranquilizer (Levanil<sup>†</sup>) afford symptomatic relief while Provera works to effect a restoration of hormonal balance. They also supplement the activity of Provera in those rare cases where restoration of hormone balance does not completely eliminate edema and anxiety/tension.

\*TRADEMARK

†TRADEMARK, REG. U. S. PAT. OFF.

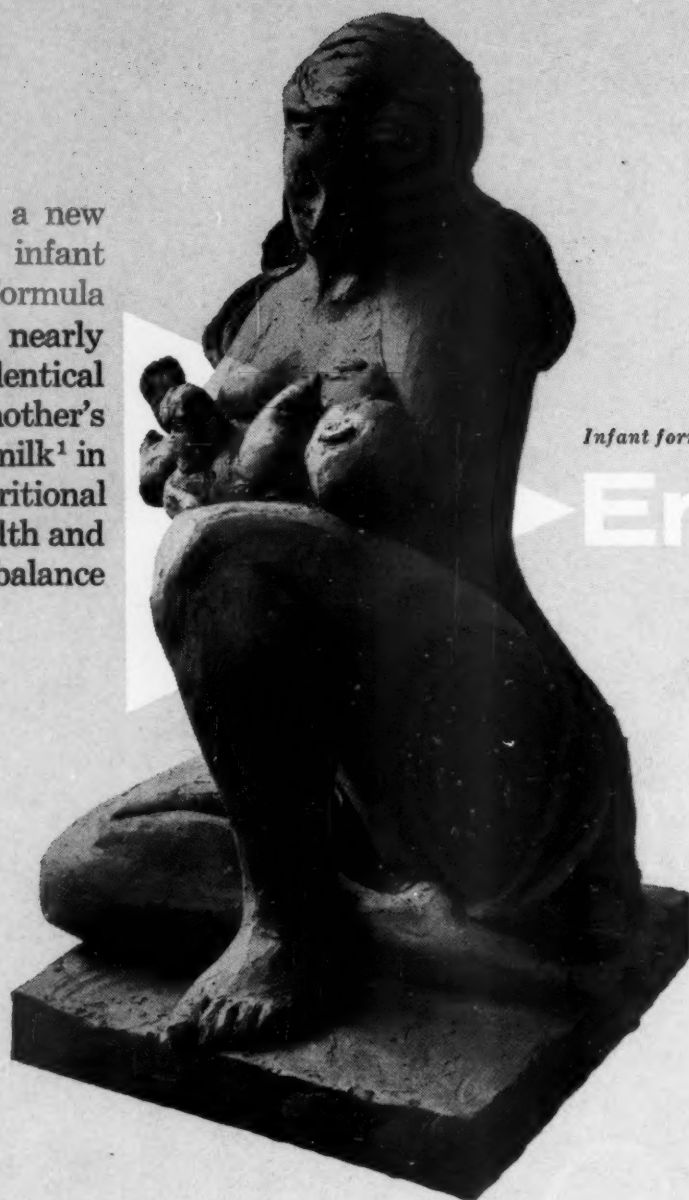


**Upjohn**

# **OF PREMENSTRUAL TENSION**



a new  
infant  
formula  
nearly  
identical  
to mother's  
milk<sup>1</sup> in  
nutritional  
breadth and  
balance



*Infant formula*

**Enfamil**

In a well controlled institutional study,<sup>2</sup> Enfamil was thoroughly tested in conjunction with three widely used infant formula products. These investigators report that Enfamil produced:

• good weight gains • soft stool consistency • normal stool frequency

1. Macy, I. G.; Kelly, H. J., and Sloan, R. E.: With the Consultation of the Committee on Maternal and Child Feeding of the Food and Nutrition Board, National Research Council: *The Composition of Milks*, Publication 254, National Academy of Sciences and National Research Council, Revised 1953. 2. Brown, G. W.; Tuholski, J. M.; Sauer, L. W.; Minsk, L. D., and Rosenstern, I.: Evaluation of Prepared Milks in Infant Nutrition; Use of the Latin Square Technique, *J. Pediat.* 56:391 (Mar.) 1960.



**Mead Johnson**  
*Symbol of service in medicine*



# 51 to 49...it's a boy!



## 94 to 6 BONADOXIN® stops morning sickness

When she asks "Doctor, what will it be?" you can either flip a coin or point out that 51.25% births are male.<sup>1</sup> But when she mentions morning sickness, your course is clear: BONADOXIN.

For, in a series of 766 cases of morning sickness, seven investigators report excellent to good results in 94%.<sup>2</sup> More than 60 million of these tiny tablets have been taken. The formula: 25 mg. Meclizine HCl (for antinauseant action) and 50 mg. Pyridoxine HCl (for

metabolic replacement). Just one tablet the night before is usually enough.

BONADOXIN—DROPS and Tablets—are also effective in infant colic, motion sickness, labyrinthitis, Meniere's syndrome and for relieving the nausea and vomiting associated with anesthesia and radiation sickness. See PDR p. 795.

1. Projection from Vital Statistics, U.S. Government Dept. HEW, Vol. 48, No. 14, 1958, p. 398.

2. Modell, W.: *Drugs of Choice 1958-1959*, St. Louis, C. V. Mosby Company, 1958, p. 347.



New York 17, New York  
Division, Chas. Pfizer & Co., Inc.  
Science for the World's Well-Being

*add to her*  
**HAPPY  
 ANTICIPATION  
 EN-CEBRIN™**



**concentrated nutritional support**

En-Cebrin provides phosphorus-free calcium . . . all known antianemia factors . . . plus important vitamins and minerals.

**one-a-day convenience and economy**

A single Pulvule® daily provides comprehensive vitamin-mineral supplementation throughout pregnancy and lactation.



**invitingly styled**

The pink-and-blue En-Cebrin Pulvules are supplied in decorative apothecary-type bottles, fashioned to enlist patient co-operation.



In special bottles of 100; also available in quantities of 5,000.

En-Cebrin™ (prenatal vitamin-mineral supplements, Lilly)

**ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U.S.A.**

012000

# American Journal of Obstetrics and Gynecology

Transactions of the Fifteenth  
Annual Meeting of the  
Society of Obstetricians and  
Gynaecologists of Canada

## Postmaturity

I. A. PERLIN, M.D., C.M., F.A.C.S., F.I.C.S., F.A.C.O.G.

Halifax, Nova Scotia

DURING the past few years, a considerable amount of controversial material has been written concerning the effects on both mother and child when a pregnancy extends beyond the expected date of delivery. The rather divided opinion has caused, at times, much concern among those who are clinically active in obstetrics. One school of thought as exemplified by Walker,<sup>12</sup> Hamilton,<sup>7</sup> Moir, etc., is rather dogmatic in suggesting that no patient should be permitted to go beyond 42 weeks of pregnancy if fetal loss is to be prevented or unduly difficult labor avoided; whereas Browne,<sup>2</sup> the Margaret Hague group, Eastman,<sup>5</sup> and Daichman and Gold,<sup>4</sup> feel that no greater ill effects will occur in the postterm patient but rather that more trouble might well arise from the

routine induction of patients who have reached beyond the forty-second week.<sup>4, 5, 8</sup>

It had been the impression in our Department at Dalhousie University that prolongation of pregnancy did not constitute a threat to mother or baby so that generally no interference was carried out and nature was allowed to take its course. During one of our refresher courses we were so intimidated by a visiting eminent obstetrician because of our attitude to so-called "postmaturity" that, as a result of his dogmatic expression of expected difficulties, within a few weeks of his lecture at least two patients were brought into the hospital for induction because they had gone more than two weeks past the expected date and both of these resulted in

*From the Department of Obstetrics and Gynecology, Dalhousie University*

*This study was made possible through the aid of a Federal Health Grant.*

*Presented at the Fifteenth Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, Mont Tremblant, Quebec, Sept. 11-13, 1959.*

Table I. Age distribution

Age (years)	Postmature		Mature	
	No.	%	No.	%
Up to 25	522	54.2	4,406	45.6
25 to 35	339	35.2	4,102	42.4
35 and above	61	6.3	746	7.7
Not clear	40	4.2	417	4.3



**Table II.** Relationship of parity to the degree of postmaturity

	<i>Mature</i>		<i>Postmature</i>							
			<i>Total</i>		<i>2-3 weeks</i>		<i>3-5 weeks</i>		<i>Over 5 weeks</i>	
	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>
Primiparas	3,870	40.0	446	46.4	299	46.3	133	47.7	14	37.8
Multiparas	5,801	60.0	516	53.6	347	53.7	146	52.3	23	62.2

**Table III.** Comparison of the incidence of hypertension in mature and postmature patients

	<i>Mature</i>		<i>Postmature</i>							
			<i>Total</i>		<i>2-3 weeks</i>		<i>3-5 weeks</i>		<i>Over 5 weeks</i>	
	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>
Normal	8,089	83.6	819	85.1	550	85.1	223	83.5	36	97.3
Hypertension	1,582	16.4	143	14.9	96	14.9	46	16.5	1	2.7

**Table IV.** Incidence of toxemia and its relationship to degree of postmaturity

	<i>Mature</i>		<i>Postmature</i>							
			<i>Total</i>		<i>2-3 weeks</i>		<i>3-5 weeks</i>		<i>Over 5 weeks</i>	
	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>
None	9,035	93.4	893	92.8	598	92.6	259	92.8	36	97.3
Severe	94	1.0	7	0.7	4	0.6	3	1.1	0	0
Mild	542	5.6	62	6.5	44	6.8	17	6.1	1	2.7
Total toxemia	636	6.6	69	7.2	48	7.4	20	7.2	1	2.7

cesarean sections because of failed induction. As a result of this, we decided to analyze critically our own cases to see whether our impressions had been correct or not.

A review of 12,000 consecutive deliveries at the Grace Maternity Hospital between 1950 and 1955 was carried out (years previous to visit mentioned above). The criterion used to identify the postmature case was by Naegle's Rule; i.e., a patient with a history of regular menstrual cycles of average duration, who remembered her last period date and whose pregnancy extended over 42 weeks was placed in the postmature group. The mature group was composed of those in the 38 to 42 weeks' range and the premature group were those under 38 weeks. Out of the 12,000 cases there were 962 so-called postmatures as compared with 9,671 matures (there were, in addition, 1,367 prematures). Of the postmatures 646 were 2 to 3 weeks, 279 were 3 to 5 weeks, and 37 were over 5 weeks postmature.

The term "postmaturity" is a troubling one, because it immediately suggests a pathological condition as far as the baby is concerned—that is, the subnourished-looking baby, with meconium-stained skin as a result of pre- or intradelivery distress—and yet this is not the usual picture when the pregnancy is prolonged. This type of baby can be seen at term and even in the premature group. It might be best, therefore, to use a term such as "prolonged pregnancy" (or, possibly, "postdate labor" as sug-

**Table V.** Position and presentation of the babies

	<i>Postmature</i>		<i>Mature</i>	
	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>
Vertex anterior	842	87.5	8,532	88.2
Vertex posterior	37	3.8	433	4.5
Brow	2	0.21	13	0.13
Face	5	0.52	22	0.23
Breech	31	3.2	306	3.2
Transverse	5	0.52	29	0.30
Unknown	40	4.2	336	3.5

Table VI. Relationship of length of labor to the degree of postmaturity

Hours of labor	Mature		Postmature							
			Total		2-3 weeks		3-5 weeks		Over 5 weeks	
	No.	%	No.	%	No.	%	No.	%	No.	%
Up to 15	6,031	62.3	575	59.8	378	58.5	171	61.3	26	70.3
15 to 25	2,117	21.9	212	22.0	157	24.3	49	17.6	6	16.2
25 and up	1,157	12.0	147	15.3	98	15.2	44	15.8	5	13.5
Not clear	366	3.8	28	2.9	13	2.0	15	5.4	0	0

gested by Daichman and Gold<sup>4</sup>). For the sake of simplicity, however, the terms "mature" and "postmature" will be used throughout this paper.

The incidence of postmaturity in this series is 8.0 per cent, which is in the range of those reporting who have used the same criterion.

#### General considerations

There were significantly a greater number of postmature patients in the younger age group (Table I).

Table VII. Incidence of uterine inertia

	Postmature		Mature	
	No.	%	No.	%
Present	22	2.3	172	1.8
Absent	919	95.5	9,207	95.2
Not recorded	21	2.2	292	3.0

It has been reported that postmaturity occurs mostly among primiparas. There were, in this series, more primiparas among the postmature group as compared to the mature group which probably coincides with the age incidence (Table II).

Within the postmature group itself, however, there were more multiparas; and this relationship was not altered by the increasing degree of postmaturity (Table II).

#### Complications of pregnancy

It has been reported that in the postmature group a large number are hypertensive during the postterm period or in labor. In this series there is little difference between the groups (in fact there is a slightly greater per cent in the mature group) (Table III).

That toxemia is a problem in the postmature patient is not reflected in this series (Table IV). There is a slight trend (7.2 to

Table VIII. Size of the baby in relation to the degree of postmaturity

Weight (pounds)	Mature		Postmature							
			Total		2-3 weeks		3-5 weeks		Over 5 weeks	
	No.	%	No.	%	No.	%	No.	%	No.	%
Under 7	3,240	33.5	207	21.5	148	22.9	53	19.0	6	16.2
7 to 9	5,729	59.2	630	65.5	418	64.7	189	67.7	23	62.2
Over 9	665	6.9	119	12.4	77	10.1	34	12.1	8	21.6
Not clearly recorded	37	0.4	6	0.6	3	0.4	3	1.1	0	-

Table IX. Size of baby in relation to parity

Weight (pounds)	Postmature				Mature			
	Primiparas		Multiparas		Primiparas		Multiparas	
	No.	%	No.	%	No.	%	No.	%
Under 7	110	24.7	97	18.8	1,523	39.3	1,713	29.5
7 to 9	301	67.5	329	63.8	2,138	55.2	3,589	61.8
Over 9	34	7.6	85	16.5	191	4.9	474	8.1
Not clearly recorded	1	0.22	5	0.97	18	0.6	25	0.4

**Table X.** Comparative incidence of fetal distress

<i>Fetal distress</i>	<i>Mature</i>		<i>Postmature</i>	
	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>
In utero	265	2.7	44	4.6
At birth				
2-5 minutes	361	3.7	41	4.3
Longer than 5 minutes	83	0.8	16	1.7

**Table XI.** Comparison of the incidence of fetal morbidity

<i>Morbidity</i>	<i>Postmature</i>		<i>Mature</i>	
	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>
Pneumonia	2	0.2	17	0.2
Atelectasis	2	0.2	26	0.3
Major feeding problem	5	0.5	19	0.2

**Table XII.** Condition of babies on discharge from hospital

	<i>Postmature</i>		<i>Mature</i>	
	<i>No.</i>	<i>%</i>	<i>No.</i>	<i>%</i>
Congenital abnormalities	24	2.5	173	1.8
Birth injuries	4	0.4	36	0.4
Stillbirth	15	1.6	94	1.0
Death	6	0.6	56	0.6

6.6—not significant) but the degree of postmaturity did not increase the amount of toxemia. However, as noted before, there were more primiparas in the postmature group which may account for the trend since 8.1 per cent of the toxemic patients of both groups were primiparas.

#### Problems of labor and delivery

There is hardly any difference in the position and presentation of the babies between the two groups (Table V). One interesting point in this series is that breech presentation was present in both groups by the same percentage and within the usually reported range of 2 to 4 per cent. Taussig and others<sup>7, 10</sup> have reported breech presentation to be rare in the postmature.

If one looks at the very long labors (over 24 hours) one notes that a slightly, though

not significantly, greater percentage of the cases were in the postmature group as compared to the mature (15.3 to 12.0); but the degree of postmaturity did not influence the number of long labors (Table VI).

#### Method of delivery

There was no difference between the two groups in the manner in which delivery was effected; 94.1 per cent of the postmature patients were delivered spontaneously or by low forceps as compared with 94.9 per cent of the mature. The cesarean section rate was about the same: 3.1 per cent of the postmature and 3.3 per cent of the mature.

Inertia is considered to be a problem when the pregnancy is prolonged. This series did not bear this out (Table VII).

#### The baby

This series did agree with the reports generally that the longer the pregnancy the bigger the baby (Table VIII). It is interesting to note, however, that more of the large babies (9 pounds and over) were in the multiparous group who generally have the easier births (Table IX).

One of the problems that has been emphasized so strongly by those who consider postmaturity a hazard has been that of fetal distress both in utero and after delivery. The rate has been quoted as being between 25 and 30 per cent.<sup>7, 12</sup> In our series there was only a small number showing signs of distress; about the same in both groups of cases (Table X).

Did the babies from the postmature group present any greater number of problems? In this series they seemed to be as healthy as the mature babies (about 99 per cent in each showed no problems) (Table XI).

The stillbirth and death rate were about the same for both groups (Table XII).

#### Comment

From this series of cases we feel that we have not erred in the past by allowing our patients to go along in their pregnancies until spontaneous labor occurred.



Since there is a normal variation in all our physiological processes, it would seem unnatural to set a specific limit of time to a normal pregnancy.

There is no doubt some danger associated with persistent induction of labor by whatever means; and if we were to follow through on the theory that pregnancy should be terminated after 42 weeks, than a failure of induction should lead to cesarean section. Here again we would be adding a real danger to both mother and child.

### Summary

1. Postmaturity is not peculiar to the primipara.

2. Our previously (and still) held concept of noninterference when the pregnancy is prolonged did not result in any greater number of mishaps to either the mother or the baby.

3. The longer the pregnancy the heavier the baby, but this does not give a valid reason for earlier induction. There were more heavier babies among the multiparas and these had generally an easier labor and fewer distress problems.

I am greatly indebted to Dr. H. B. Atlee, Professor Emeritus, and Dr. C. B. Stewart, Dean of Dalhousie Medical School, for their advice as to material and statistics.

### REFERENCES

1. Bancroft-Livingstone, G., and Neill, D. W.: *J. Obst. & Gynaec. Brit. Emp.* 64: 498, 1957.
2. Browne, F. J.: *Brit. M. J.* 1: 851, 1957.
3. Calkins, L. A.: *AM. J. OBST. & GYNEC.* 68: 50, 1954.
4. Daichman, J., and Gold, E. M.: *AM. J. OBST. & GYNEC.* 68: 1128, 1954.
5. Eastman, N. J.: *Obst. & Gynec. Surv.* 12: 476, 1957.
6. Gibberd, C. F.: *Lancet* 1: 64, 1958.
7. Hamilton, C. J. K.: *Brit. M. J.* 2: 281, 1950.
8. Koosterman, G. J.: *Obst. & Gynec. Surv.* 12: 470, 1957.
9. Racker, Dudley: *Lancet* 2: 953, 1953.
10. Taussig, F. J.: *AM. J. OBST. & GYNEC.* 44: 516, 1901.
11. Theobald, G. W.: *Lancet* 1: 59, 1959.
12. Walker, J.: *J. Obst. & Gynaec. Brit. Emp.* 61: 162, 1954.

# Internal hemorrhage following gynecological operations

ROBERT H. WESLEY, M.D., F.R.C.S. (C.)

*Toronto, Ontario*

SEVERE continuing internal hemorrhage following major gynecological operations is a rare complication. In the Toronto Western Hospital, in the 10 year period ending Dec. 31, 1957, there were 9 cases occurring in approximately 5,400 major gynecological procedures. Most postoperative hemorrhages present as frank vaginal bleeding, and the diagnosis is easily made and the problem may be dealt with quickly. However, a far more sinister and dangerous event arises when there is no external sign of hemorrhage. Such hemorrhage may be intraperitoneal or extraperitoneal, early (that is within 12 hours) or delayed. Jeffcoate<sup>2</sup> classifies as primary those within 24 hours and, secondary, from the eighth to the fourteenth day. Since the terms "primary" and "secondary" have been so abused in medical teaching, it is felt that early and delayed are more descriptive.

Table I shows the age, diagnosis, operative procedure, cause of bleeding, and the treatment instituted. All patients were under the care of the attending staff. All were in the reproductive period and the ages varied from 29 to 50, the average being 38.5 years. Six of the operations were performed for genital prolapse, one for fibroids, one for ovarian cyst, and one for endometriosis. Five of these patients were found to have retroperitoneal bleeding. Three bled intraperitoneally and in one the source of bleeding was never determined.

*From the Toronto Western Hospital.  
Presented at the Fifteenth Annual  
Meeting of the Society of Obstetricians  
and Gynecologists of Canada, Mont  
Tremblant, Quebec, Sept. 11-13, 1959.*

There are two crucial periods. One is the time it takes to make the diagnosis and the other, the time it takes to correct the blood loss and stop the bleeding. If the diagnosis is delayed too long, as in one case, death will result. Delay in treatment resulted in another fatality.

## Diagnosis

These patients may still be under anesthesia or just regaining consciousness. The diagnosis is therefore difficult and should be made in the recovery room or on the ward in the early postoperative period. In this group, the average time until symptoms became obvious was 7 hours. The time from the start of the initial procedure until operation or death varied between 4½ hours and 18 hours, the average being 11 hours.

There are only two constant signs which are of value. These are a persistent rapid weak pulse and persistent low blood pressure. Contrary to popular belief, a slow pulse was not found in any instance. The pulse rate varied from 90 to 180 per minute. Blood pressure varied from complete absence of any systolic or diastolic pressure to 80/60. Typical, predictable pulse and blood pressure findings were therefore constant. Table II illustrates this.

Changes in color, skin temperature, and respirations are not necessarily indicative of hemorrhage in a patient still under anesthesia or in the immediate postoperative period. Abdominal findings are confusing and unreliable, especially if the hemorrhage is retroperitoneal. Large amounts of free intraperitoneal blood will simplify the diagnosis. The

difficulty is to rule out other causes of collapse. Early surgical shock responds quickly and permanently to sedation and blood transfusion. Continuing concealed hemorrhage does not.

Other more common causes of peripheral vascular collapse must be quickly eliminated. In one case, immediate electrocardiography was carried out to eliminate coronary occlusion. The initial drop in blood pressure associated with a perforated peptic ulcer will respond rapidly and not continue to drop as in uncontrolled blood loss. The most accurate and encouraging diagnostic procedures for future emergencies are the newer methods for estimating the blood volume.<sup>1, 3</sup> These methods can measure the blood volume within 200 c.c. and can be reported within 20 minutes. Repeated blood volume estimations would therefore be of incalculable value where concealed hemorrhage is suspected. If, in addition, an accurate record is kept of blood loss during the operation by such a simple method as weighing the

sponges and this is charted against replacement, a diagnosis can be arrived at very quickly.

#### Treatment

The treatment of early severe internal hemorrhage is specific and curative. Adequate early blood replacement up to the amount lost, with immediate laparotomy to stop the bleeding, is the only method of value. Delay, in the hope that the bleeding will stop by itself, can be fatal. Peering into the vagina in an attempt to stop supravaginal bleeding is a waste of time, but packing, if present, should be removed. At laparotomy one may be fortunate enough to find a bleeding vessel which a ligature or suture will quickly control. It is far more likely that a massive retroperitoneal hematoma will be found which is semiadherent and is produced by constant oozing from a large surface. Jeffcoate<sup>2</sup> reports that intrapelvic hemorrhage is nearly always the result of a slipped ligature on the ovarian or uterine vessels.

Table I. Causes of hemorrhage and methods of treatment

Case	Age	Diagnosis	Operation	Cause of bleeding	Treatment
1	37	Fibroids	Total hysterectomy	General oozing, intraperitoneal	Laparotomy, intra-abdominal packing
2	35	Prolapse	Vaginal hysterectomy and repair	Base of bladder, extraperitoneal	Laparotomy suturing
3	44	Fibroids prolapse	Vaginal hysterectomy and repair	Not known	Transfusion
4	29	P.I.D.; right ovarian cyst	Right oophorectomy suspension	Right ovarian artery, intraperitoneal	Laparotomy, ligation, salpingectomy
5	40	Prolapse menorrhagia	Vaginal hysterectomy and repair	Retroperitoneal oozing	Laparotomy; late, unable to control
6	31	Prolapse	Vaginal hysterectomy and repair	Retroperitoneal oozing	Laparotomy, suturing
7	37	Prolapse	Spalding-Richardson repair	Base of bladder, retroperitoneal	Laparotomy, left uterine artery
8	50	Prolapse fibroids	Vaginal hysterectomy and repair	Left ovarian artery	Laparotomy, ligature
9	44	Pelvic endometriosis	Total abdominal hysterectomy	Retroperitoneal oozing	Laparotomy, suturing



Table II. Clinical data on time and signs of circulatory collapse and outcome

Case	Elapsed time to collapse (hours)	Elapsed time to second operation (hours)	Average pulse	Average blood pressure	Transfusion (c.c.)	Recovery
1	9	15	140	Absent	2,000	Good
2	6	8	108	80/50	2,000	Good
3	6	9	120	80/60	Less than 500	Died
4	10	11½	118	68/36	1,500	Good
5	11	18	90	50/0	4,500	Died
6	2½	4½	180	80/60	3,000	Good
7	6½	13	150	80/40	2,500	Good
8	7	9½	90	80/60	4,500	Good
9	5½	9½	100	90/70	3,500	Ureter tied, eventual nephrectomy

His suggestion that retroperitoneal retraction of an ovarian vessel causes extravasation of blood into the tissues is probably correct. The hematoma is certainly retroperitoneal and the peritoneum must be incised. However, finding and securing a bleeding point may be impossible. It is even doubtful if ligation of the anterior branch of the internal iliac artery will be sufficient, in view of the anastomoses in the area and the complicating widespread venous oozing.

In the few cases under review, pressure, Gelfoam, suturing, and even packing were used. Radical measures are in order and through-and-through deep sutures may be necessary to save a life even at the risk of damaging a ureter. In several cases ligation of major vessels was considered but was not thought to be necessary or of value. If packing is to be used it should be placed securely and deeply, left in for a brief period, and removed through the vaginal vault.

In this series the blood required varied from less than 500 c.c. to 4,500 c.c. The average amount was 2,600 c.c.

It might be of value to review quickly the histories of the 2 patients who died and the one who suffered a major complication.

Case 3. A 44-year-old multipara with fibroids and prolapse underwent a difficult vaginal hysterectomy and repair. Collapse occurred within 6 hours of the start of the procedure but was not immediately recognized by inexperienced

attendants. Neither the resident nor the staff gynecologist was alerted in time, and within 9 hours she was dead. Attempts to administer adequate amounts of blood to this moribund patient were unsuccessful and it was possible to pump less than 500 c.c. into the collapsed veins.

Case 5. A 40-year-old multipara with prolapse and menorrhagia underwent an uneventful vaginal hysterectomy and repair. Collapse was delayed for 11 hours and was treated by blood transfusion. It was decided that a conservative regime should be followed and she was watched carefully for 7 hours. She did not rally, and a laparotomy was performed after 18 hours. Time was against the surgeons. They were unable to control the bleeding and she died on the operating table after receiving 4,500 c.c. of blood.

Case 9. A 44-year-old nulliparous patient underwent an extremely difficult total abdominal hysterectomy for advanced pelvic endometriosis. During the procedure considerable bleeding was encountered from the left pelvic wall. Laparotomy 9½ hours later revealed widespread oozing from this area which was eventually controlled by deep suturing. The left ureter was unfortunately included in the sutures and, after a prolonged period of discomfort, investigation, and hospitalization, a left nephrectomy was necessary. This case serves to further illustrate the problem of hemorrhage associated with operation for endometriosis.

#### General comments

Early concealed continuing hemorrhage following major gynecological operations is a rare but serious complication. From the

onset of collapse every effort must be made to provide the diagnosis rapidly by the methods outlined and perhaps by means of the newer blood volume procedures, if they are available.

Treatment consists of adequate blood re-

placement and rapid emergency laparotomy to control the hemorrhage.

In conclusion, I should like to mention that a review of the recent literature failed to unearth any reports on this serious and possibly fatal complication.

---

#### REFERENCES

1. Benson, S. A.: Bull. New York Acad. Med. 30: 750, 1954.
2. Jeffcoate, T. N. A.: Principles of Gynaecology, London, 1957, Butterworth & Co., Ltd.
3. Veall, N. C., and Vetter, H.: Radioisotope Techniques in Clinical Research and Diagnosis, London, 1958, Butterworth & Co., Ltd.

# Placenta previa

A critical appraisal of eight years' management

WILLIAM R. FOOTE, M.D., F.R.C.S. (C.)

WILLIAM DENNIS FRASER, M.D., F.R.C.S. (C.)

Montreal, Quebec

THIS review was prompted by a desire to evaluate our management of placenta previa with the hope of improving fetal salvage, particularly in the low-lying type of placenta previa.

## Material and sources

Our series of cases is taken from the records of the Royal Victoria Montreal Maternity Hospital for the years 1950 to 1957, inclusive.

## Incidence

There were 26,470 deliveries at the hospital during the same period. Three hundred and thirty-eight or 1.3 per cent of the patients had third trimester bleeding, and of these 120 or 0.45 per cent had placenta previa (Table I). This incidence is similar to that quoted by others.<sup>1-4</sup>

## Classification

In discussing placenta previa, the problem of classification arises immediately. There is also a need for consistent terminology. Confusion arises, for example, from the terms "marginal" and "lateral" which are interchangeable. Where there is cervical dilatation, a central placenta previa becomes separated at one edge and feels like a tongue projecting over or into the cervix,

which may lead to the designation of a partial, rather than a central, placenta previa.

Various authorities have described several classifications as follows:

Eastman<sup>5</sup>:

1. Total placenta previa: totally covers the internal os.
2. Partial placenta previa: partially covers the internal os.
3. Low implantation: placenta does not extend beyond the margin of the internal os.

Kerr<sup>6</sup>:

1. Central, complete, or total: implantation covers internal os so that margin of placenta cannot be felt.
2. Marginal: the margin of the placenta can easily be felt.
3. Lateral: the margin of the placenta does not reach down to the os internum and can be felt only with difficulty by the examining finger.

Macafee<sup>7</sup> and Browne<sup>8</sup>:

1. First degree: the greater part of the placenta is in the active contractile or upper segment, and only the lower margin is in the lower segment.
2. Second degree: the margin reaches down to the internal os.
3. Third degree: the placenta covers the internal os when closed, but not entirely when dilated.
4. Fourth degree: the central part of the placenta covers the os internum.

The incidence of the three varieties of placenta previa in our series and in several others is shown in Table II. We have trans-

*From the Royal Victoria Montreal Maternity Hospital.*

*Presented at the Fifteenth Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, Mont Tremblant, Quebec, Sept. 11-13, 1959.*



posed the classifications in each series to conform to Eastman's classification.

Comparison of these series shows a wide variation in the types diagnosed, especially with regard to partial and complete placenta previa. The figures for the low-lying variety, however, are fairly uniform. The discrepancies would seem to demonstrate the problems previously outlined with regard to diagnosis and classification.

### Predisposing factors

Placenta previa occurs four times more frequently in multiparas (Table III). This incidence is the same as that reported by Berkeley,<sup>14</sup> Semmens,<sup>15</sup> and Schmitz.<sup>16</sup> There was almost twice the frequency of placenta previa in those over age 29 compared to those under 29 years of age.

Chronic subinvolution and defective vascularization may be predisposing factors, since 40 of our patients had recorded postpartum uterine infection (endometritis and parametritis) during preceding pregnancies.

### Clinical features

**Hemorrhage.** Bleeding may occur at any time from the fourteenth week onward, or not until there is a profuse hemorrhage during labor at term (Table IV).

In the present series, the majority of patients (79 per cent) suffered the first blood loss after the thirty-second week, and 52 per cent of all placenta previas of the total variety had the first loss of blood in the last 4 weeks of pregnancy. Sixty per cent of the

Table I. Frequency and causes of third trimester bleeding\*

Placenta previa	120
Accidental hemorrhage	127
Marginal sinus rupture	8
Cervical bleeding	12
Placental anomalies	4
Vaginal varices	1
Ruptured chocolate cyst	1
Undiagnosed	65
Total	338

\*Total deliveries, 26,470; incidence of third trimester bleeding, 1.3 per cent; incidence of placenta previa 0.45 per cent, or 1 in 220.

Table II. The incidence of varieties of placenta previa

	Total	Low-lying (%)	Partial (%)	Complete (%)
Royal Victoria Hospital	120	55.8	11.7	32.5
Phillips <sup>9</sup>	143	55.3	36.3	8.4
King and Chun <sup>10</sup>	134	44.0	40.0	16.0
Johnson <sup>11, 12</sup>	201	54.0	18.0	28.0
Gutierrez-Yepes <sup>13</sup>	304	48.0	29.0	23.0
Hatten et al. <sup>4</sup>	59	46.0	17.0	37.0

Table III. Predisposing factors

	Total		Low-lying	Partial	Complete
	No.	%			
Age					
Under 29	44	36.6	28	3	13
Over 29	76	63.6	39	10	27
Nulliparas	26	22	18	3	5
Multiparas	88		47	10	31
Grand multiparas	6	78	2	0	4

patients bled only a mild to moderate amount.

**Pain.** Although placenta previa is described classically as being attended by painless hemorrhage per vaginam, 16 per cent of the series was associated with abdominal pain and uterine tenderness (other than that typical of labor or false labor), and, of these, one half of the cases involved total placenta previa (Table V).

**Presentation.** There were 51 patients with abnormal presentation of the presenting part (Table VI). Fifteen (12.5 per cent) were shoulder presentations compared to the incidence of 0.34 per cent with a normally implanted placenta (a finding similar to that of Semmens<sup>15</sup> and others<sup>17, 18</sup>).

**Toxemia.** There was not a single occasion of toxemia of pregnancy in the group of 120 cases, although the absence of toxemia is said not to exclude placenta previa.<sup>19, 20</sup>

**Multiple pregnancy.** There were 5 cases of multiple pregnancy, all of which were twin pregnancies. The incidence (4.1 per cent) is higher than that quoted by Eastman.<sup>5</sup>

**Table IV. Hemorrhage**

	Total	Low-lying	Partial	Complete
<i>Gestation time at onset of first bleeding</i>				
Less than 28 weeks	10	6	0	4
28-32 weeks	15	4	3	8
32-36 weeks	28	18	2	8
36-40 weeks	67	39	6	22
In labor	33	27	4	2
<i>Amount of blood loss</i>				
Mild (less than 100 c.c.)	47	28	6	13
Moderate (100-500 c.c.)	59	36	5	18
Severe (500 c.c. with fall in blood pressure)	14	3	3	8

**Table V. Pain and tenderness**

	Total	Low-lying	Partial	Complete
Painless	101	0	0	0
Abdominal pain and tenderness	19	10	0	9

**Anemia and uterine anomalies.** These are mentioned because of their occurrence in this series.

#### Management

After review of the literature on placenta previa, it becomes apparent that expectant treatment has become the favored therapy in most clinics.

Prior to 38 weeks of gestation, those who were admitted to our unit were treated expectantly, unless the vaginal bleeding was of such proportions as to force immediate surgical intervention. Table VII reveals that fully 39 per cent of patients were treated by bed rest in the hospital for a period of one to 4 weeks. Almost one half of these patients were kept in the hospital for periods longer than 4 weeks, in an attempt to reach a stage of infant viability and reasonable infant risk.

The primary episode of bleeding was found to cease within 2 to 3 days with bed rest and sedation in the vast majority of cases. When bleeding ceased, a gentle vaginal speculum examination was performed to rule out local causes of bleeding, and, more spe-

cifically, malignant involvement of the lower genital tract. This examination was carried out in the delivery room under sterile conditions.

If the vaginal bleeding occurred after the thirty-eighth week, during labor, or prior to the thirty-eighth week and was of such proportions that expectant therapy was contraindicated, the patient was cross-matched for 1,000 c.c. of blood and taken to the operating room with blood running intravenously for a vaginal examination under anesthesia. A double instrument set was available for vaginal or cesarean section delivery, whichever might have been required.

**Placentography.** Many writers<sup>18, 21-24</sup> estimate that there is 90 per cent accuracy in locating the placental site. In our clinic, placentography by the soft tissue technique has proved to be of only questionable value.

**Table VI. Other clinical features**

	Total	Low-lying	Partial	Complete
<i>Abnormal presentations</i>				
Floating head	24	7	5	12
Transverse lie	15	8	2	7
Occipitoposterior	8	8	0	0
Breech	4	4	0	0
Toxemia	0	0	0	0
Multiple pregnancy (twins)	5	4	0	1
Anemia (preceding bleeding)	4	2	0	2
Uterine anomaly (1 bicornuate, 1 didelphys)	2	1	1	0
Trauma (A.R.M.)	1	1	0	0
Fibromyoma uteri	1	1	0	0

**Table VII. Expectant treatment and management**

Weeks of bed rest	Total	Low-lying	Partial	Complete
Less than 1 week	72	35	5	32
1 to 4 weeks	33	22	6	5
4 weeks or more	15	10	3	2

}39%

**Table VIII.** The use of blood transfusion

	<i>Low-lying</i>	<i>Partial</i>	<i>Complete</i>
Ante partum	5	0	2
With cesarean section or post partum	23	9	36

**Table IX.** Mode of delivery

	<i>Total</i>	<i>Low-lying</i>	<i>Partial</i>	<i>Complete</i>
Delivered per vaginam	48 (40%)	48	0	0
Artificial rupture of membranes	48	48	0	0
Pitocin drip	5	5	0	0
Spontaneous	25	25	0	0
Forceps	18	18	0	0
Breech (all assisted)	5	5	0	0

Thirty of 120 patients were x-rayed. We were successful in locating 17 low-lying placentas, but failed to diagnosis 3 partial and 10 complete placenta previas.

**Supportive measures.** In our group 62.5 per cent had a blood transfusion. This is a minimal incidence compared to that of 85 per cent quoted by Reich.<sup>18</sup> Thirty-six patients of 39 with complete placenta previa were given transfusions during and after cesarean section (Table VIII).

**Method of delivery.** Of 120 patients diagnosed as having placenta previa, 48 were delivered vaginally after rupture of the forewaters. Only 5 cases were recorded in which Pitocin was used to stimulate labor (Table IX).

All of the patients delivered vaginally had a placenta described as of the low-lying variety. Seventy-two patients were delivered by cesarean section, 19 of which had a low-lying placenta. All of the latter cases were associated with heavy vaginal bleeding.

There were no versions, extractions, or other forms of vaginal interference, except in one patient who was treated by introduction of a vaginal pack prior to admission. (She was delivered per vaginam of a still-born baby and a low-lying placenta.)

The incidence of vaginal delivery (40 per

cent) and cesarean section (60 per cent) compares favorably with figures quoted by authors of other modern series (Table X).

**Type of cesarean section.** Table XI reviews the incidence and type of cesarean section performed in the series. Sixty-four per cent of the sections were lower segment type. Low vertical and classical uterine incisions were performed to avoid anteriorly situated placentas and large varicosities in the retrovesical area.

Many clinics<sup>17-19, 21, 24</sup> advocate the low transverse approach because of the safe uterine scar allowing for delivery per vaginam in subsequent pregnancies. Others such as Johnston,<sup>26</sup> of the Texas Postgraduate School, warn against this type of incision if it involves the placental site, stressing the danger of fetal blood loss, especially in the premature infant. When unavoidable, this author stresses immediate transfusion of the baby as a lifesaving procedure. Two of our premature infants were extracted through the placenta and both died. Perhaps the cord should have been clamped prior to extraction, immediate blood studies done, and replacement instituted if necessary.

**Anesthesia.** Ninety-three per cent of cesarean sections were performed with the aid

**Table X.** Incidence of vaginal versus cesarean section deliveries in placenta previa

	<i>Vaginal (%)</i>	<i>Cesarean section (%)</i>
Royal Victoria Hospital	40	60
Reich <sup>18</sup>	15	85
Kimbrough <sup>21</sup>	30	70
Smith <sup>22</sup>	39	61
Hibbard <sup>3</sup>	25	75
Green <sup>25</sup>	19	81

**Table XI.** Type of cesarean section

Classical incision	26
Lower segment transverse	27
Lower segment vertical	19
Cesarean hysterectomy	1
(marginal placenta previa with postpartum hemorrhage and afibrinogenemia)	

64%



Table XII. Anesthesia

Type	Vaginal delivery	Cesarean section	Total
Local	1	—	1
General	37	5	42
Spinal	10	67 (93%)	77

Table XIII. Maternal morbidity

Pyelonephritis	2
Cystitis	2
Endometritis, metritis, parametritis	23
Thrombophlebitis	1
Ileus	1
Wound separation	1
Afibrinogenemia	1
Total	31* (26%)

\*Ten low-lying (all vaginal deliveries), 5 partial, 16 complete.

of a spinal anesthetic. This is in keeping with the general policy of this clinic, where it is felt, that an infant delivered by the abdominal route suffers less insult when conduction anesthesia is employed (Table XII).

### Results

**Maternal mortality and morbidity.** There were no maternal deaths in this series.

Morbidity occurs in a patient whose temperature is 100.4° F. or over after the first 24 hours postpartum. Twenty-six per cent of the patients were thus classified, a favorable figure compared to those of clinics which exclude the first 3 days after cesarean section<sup>18</sup> (Table XIII).

The most common occurrence was endometritis occurring most frequently in the patient with the complete type of placenta previa.

These figures demonstrate again the vulnerability of the patient with placenta previa and subsequent blood loss to the ravages of puerperal sepsis.

**Fetal salvage.** Of the 120 cases in the series, 110 babies were alive and well from 106 deliveries. Fifteen died from the remaining 14 deliveries, giving an over-all total uncorrected perinatal mortality of 12.5 per cent (Table XIV).

Table XV reviews the fetal deaths and compares them to the length of gestation and type of delivery. Of the 15 infant deaths, 9 occurred among those delivered vaginally (and 2 of these were less than 28 weeks' gestation), giving an uncorrected fetal mortality rate of 18.7 per cent with vaginal delivery.

Six infant deaths occurred among those delivered by cesarean section (and all of these were less than 28 weeks' gestation), giving an uncorrected fetal mortality of 8.3 per cent with delivery by cesarean section.

It is quite possible that fetal salvage may be further improved when viable babies in cases of low-lying placenta are delivered by cesarean section rather than per vaginam.

### Comment

The rationale of present-day conservative management in placenta previa in a well-organized obstetric unit is to allow bad risk, immature, and premature infants to gain valuable maturity in utero without jeopardy to the mother. The results of expectant therapy reviewed in this paper are much superior to those of bygone days when this condition was considered an obstetrical emergency requiring immediate intervention.

Table XIV. Analysis of surviving infants

	Mature		Premature		Immature		Total
	Vaginal delivery	Cesarean section	Vaginal delivery	Cesarean section	Vaginal delivery	Cesarean section	
Low-lying	21	9	21	9	1	—	61
Partial	—	6	—	6	—	1	13
Complete	—	15	—	20	—	1	36
Total	51		56		3		110*

\*One hundred six deliveries; twins account for extra 4 infants.

Table XV. Perinatal loss (type of delivery versus maturity)\*

	Mature		Premature		Immature		Total
	Vaginal delivery	Cesarean section	Vaginal delivery	Cesarean section	Vaginal delivery	Cesarean section	
Low-lying	3†	—	4†	—	2‡	—	9
Partial	—	—	—	—	—	—	—
Complete	—	—	—	2†	—	4§	6
Total	3		6		6		15

\*Uncorrected fetal mortality, 12.5 per cent.

†Postpartum deaths.

‡One intrapartum, one postpartum death.

§Two antepartum, 2 postpartum deaths.

||Fourteen deliveries; 1 twin died.

Other local causes of vaginal bleeding in the last trimester are easily ruled out by gentle inspection with use of the speculum, once the bleeding has subsided.

A high degree of suspicion should accompany those cases of bleeding associated with abnormal presentation, multiparity, increased age of the mother, and previous uterine infections. Abdominal pain and tenderness do not rule out the possibility of placenta previa, nor does the lack of associated toxemia help to confirm the diagnosis.

One may suspect the complication by findings which suggest the pathologic condition in soft tissue films of the pelvis.

A positive diagnosis is made only by vaginal examination under anesthesia, and, less often (at least in our hands), by placentography. We do not decry the use of placentography, for we have found it to be an invaluable aid in diagnosis in some cases.

The tendency to higher cesarean section rates, even for marginal placenta previa, is attended by a greater percentage of liveborn infants who survive. Surgical procedures do leave weaker uteri for subsequent pregnancies, but in our clinic pregnancies subsequent to cesarean section are delivered by repeat cesarean section. The all-important decision is to ascertain the time and method of delivery which will afford the viable infant the most advantageous entrance into the world. We believe that a lower perinatal mortality rate demands an increase in the incidence of cesarean section over that which prevails in today's clinics.

Adequate transfusion, the availability of specific antibiotics, and the use of conduction anesthetics are all-important implements in the armamentarium which will lower maternal morbidity and fetal morbidity and mortality.

Finally, a competent team is mandatory to supervise the aftercare of the newborn in order to ensure a low neonatal mortality.

### Summary

One hundred and twenty cases of placenta previa occurred in 26,470 deliveries at the Royal Victoria Montreal Maternity Hospital.

Age, parity, and subinvolution seem to be predisposing factors.

Hemorrhage was associated with abdominal pain in 16 per cent of cases.

There was a thirty-five-fold increase in the incidence of shoulder presentation and a surprising lack of associated toxemia.

Placentography is of no special value as an aid to diagnosis in our hands.

Thirty-nine per cent of patients were treated by bed rest for a period of one to 4 weeks.

Sixty-five per cent of patients required transfusion, and 26 per cent of cases were complicated by puerperal sepsis of one form or another.

The cesarean section rate was 60 per cent; 93 per cent were performed under spinal anesthesia.

There were no maternal deaths. The overall uncorrected fetal mortality rate was 12.5

per cent. We believe this incidence might be further decreased by abdominal delivery of

viable infants associated with low implanted placenta previa.

#### REFERENCES

1. Beilly, J. S., Greenberg, M. M., Aaron, J. B., and Peck, S. J.: *AM. J. OBST. & GYNEC.* 63: 414, 1952.
2. Davidson, V. A., and Brunken, R.: *J. Internat. Coll. Surgeons* 27: 466, 1957.
3. Hibbard, L. T.: *Obst. & Gynec.* 8: 613, 1956.
4. Hatten, J. Q., Kirkpatrick, S. A., and Thornton, W. N., Jr.: *AM. J. OBST. & GYNEC.* 70: 1181, 1955.
5. Eastman, N. J.: *Williams' Obstetrics*, ed. 11, New York, 1956, Appleton-Century-Crofts, Inc., p. 673.
6. Kerr, J. M. Munro: *Operative Obstetrics*, ed. 6, London, 1956, Ballière, Tindall, and Cox, Ltd., p. 755.
7. Macafee, C. H. G.: *J. Obst. & Gynaec. Brit. Emp.* 52: 313, 1945.
8. Browne, F. J.: *Antenatal and Postnatal Care*, London, 1944, J. & A. Churchill, Ltd.
9. Phillips, L. G.: *Proc. Roy. Soc. Med.* 39: 552, 1946.
10. King, G., and Chun, D.: *Brit. M. J.* 1: 9, 1945.
11. Johnson, H. W.: *AM. J. OBST. & GYNEC.* 50: 248, 1945.
12. Johnson, H. W.: *AM. J. OBST. & GYNEC.* 59: 1236, 1950.
13. Gutierrez-Yepes, L., and Eastman, N. J.: *South. M. J.* 39: 291, 1946.
14. Berkeley, Comyns: *J. Obst. & Gynaec. Brit. Emp.* 43: 393, 1936.
15. Semmens, J. P.: *AM. J. OBST. & GYNEC.* 77: 63, 1959.
16. Schmitz, H. E., O'Dea, N. J., and Isaacs, J. H.: *Obst. & Gynec.* 3: 3, 1954.
17. Findley, D.: *AM. J. OBST. & GYNEC.* 36: 267, 1938.
18. Reich, A. M.: *AM. J. OBST. & GYNEC.* 72: 277, 1956.
19. Lewis, T. L. T.: *Progress in Clinical Obstetrics and Gynaecology*, London, 1956, J. & A. Churchill, Ltd.
20. Friedman, E. A., and Little, W. A.: *AM. J. OBST. & GYNEC.* 76: 919, 1958.
21. Kimbrough, R. A.: *AM. J. OBST. & GYNEC.* 78: 1161, 1959.
22. Smith, K.: *AM. J. OBST. & GYNEC.* 77: 55, 1959.
23. Dipple, A. L., and Brown, W. H.: *AM. J. OBST. & GYNEC.* 40: 986, 1940.
24. Stallworthy, J. A.: *Tr. Am. Assn. Obst. & Gynec.* 61: 9, 1950.
25. Green, G. H.: *J. Obst. & Gynaec. Brit. Emp.* 66: 640, 1959.
26. Johnston, R. A.: *AM. J. OBST. & GYNEC.* 72: 683, 1956.



# A clinical analysis of abruptio placentae

MYER HENDELMAN, M.D., F.R.C.S. (C.)

WILLIAM DENNIS FRASER, M.D., F.R.C.S. (C.)

*Montreal, Quebec*

THIS paper deals with a review of antepartum hemorrhage at the Royal Victoria Montreal Maternity Hospital from 1950 to 1957, inclusive. During this period there were 126 cases diagnosed as abruptio placentae out of the 328 cases of late trimester bleeding in a total of 26,470 deliveries. Our incidence of 0.48 per cent (or 1 in 208 cases) is practically the same as the incidence of Daro and associates<sup>1</sup> in 72,000 deliveries at the Cook County Hospital (0.42 per cent) and that of Bieber<sup>2</sup> reported in his review of 79,000 deliveries at the New Orleans Charity Hospital (0.4 per cent). In our series, it accounted for 38.4 per cent of cases of third trimester bleeding.

The cases (Table I) were divided into (a) mild, (b) moderate, and (c) severe, according to the classification of Sexton and associates.<sup>3</sup> The mild, numbering 58, are characterized by external bleeding of less than 400 c.c., little pain or other evidence of concealed hemorrhage, and involvement of not more than one sixth of the placental surface. Twenty-seven, or nearly 50 per cent, of these patients were in labor at the time of the hemorrhage.

The moderate cases of abruptio placentae numbered 54. The criteria for this group were: (1) external hemorrhage of more than 400 c.c. or evidence of concealed hemorrhage as manifested by variable pain, ab-

dominal and uterine tenderness, spasm, and rigidity; (2) a distressed or lost fetal heart-beat; and (3) the finding post partum of one sixth to two thirds of the placental surface involved in old or recent clot formation.

There were 14 severe cases of abruptio placentae with 5 showing evidence at operation of the extreme form of abruptio placentae clinically known as the Couvelaire uterus. The clinical manifestations in the severe group are extreme forms of the symptoms and signs noted for the moderate group plus clinical shock, often out of proportion to the external blood loss. It is in this group that the major maternal complications of renal failure, hypofibrinogenemia, and death are apt to be found.

## Special clinical points

Our series was remarkable in only one finding, i.e., the very low incidence of associated toxemia of pregnancy. Whereas most series show an associated antecedent toxemia ranging from 20 per cent to as high as 50 per cent, we had only 14 patients with a diagnosis of toxemia of pregnancy, or 11 per cent. Both this low figure and our rather low general incidence of abruptio placentae of 1 in 208 cases may be related to the declining incidence of toxemia in our clinic which has dropped from about 10 per cent in 1940 to the present 3 to 4 per cent.

Other pertinent findings in our analysis were: (1) 54 per cent of cases occurred in the over-29 age group; (2) 62.7 per cent were in multiparas, 10 per cent of which were grand multiparas; (3) 58 of the 126

*From the Royal Victoria Montreal Maternity Hospital.*

*Presented at the Fifteenth Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, Mont Tremblant, Quebec, Sept. 11-13, 1959.*

patients presented in labor; (4) pain was either absent or not noted in our records in 41 cases, or 32 per cent, but in the majority of these bleeding was external, with mild or small recurring hemorrhages.

### Management

The management of abruptio placentae requires active intervention in the majority of cases. The primary requisites agreed to by all are: (1) to replace blood loss, both external and concealed, as evidenced by shock out of proportion to the visible blood loss; (2) to test repeatedly for the development of hypofibrinogenemia and for the adequacy of the patient's clot formation and clot stability; (3) to give morphine sulfate as indicated for the relief of pain; (4) to rupture the membranes on diagnosis of abruptio placentae, whether ultimate delivery is to be by vaginal route or by cesarean section. The giving of Pitocin at this point is controversial but the majority of authors are in favor of its judicious use.

The next step in management is our most important decision, and it is subject to conflicting opinion. Some observers believe that vaginal delivery is preferable, some that a high cesarean section rate improves both maternal welfare and fetal salvage, particularly the latter. The consensus is that the shorter the period of time from the acute

onset of abruptio placentae until ultimate delivery, the less is the likelihood of development of some of the dreaded maternal complications or of losing a baby whose fetal heartbeat is present on admission to hospital. Eastman<sup>4</sup> states that "cesarean section becomes desirable in cases in which artificial rupture of membranes does not bring about delivery within 10 or 12 hours." Weiner and his associates<sup>5</sup> contend that the first hour should be dedicated to the assessment of the patient, the giving of blood, and the use of morphine sulfate and atropine for the control of pain if necessary. In the second hour, examination and rupture of membranes is carried out and hourly clot observations instituted. If bleeding persists or the baby shows distress or delivery is not anticipated within 4 to 12 hours, a cesarean section is indicated. Bysshe,<sup>6</sup> from the Sloane Hospital, and Douglas and associates,<sup>7</sup> from the New York Lying-In Hospital, both agree to a 6 hour limit. Douglas and co-workers<sup>7</sup> point out, in addition, that, if a cesarean section had been done in all cases within 3 hours, many of their babies that died in labor could theoretically have been saved.

Our management in this present series follows fairly closely the above principles. Forty-four patients were given transfusions (that is, before delivery), and only one patient required fibrinogen. Examinations were

Table I. Classification and incidence

	Mild	Moderate	Severe
No. of cases	58	54	14
Amount of hemorrhage	< 400 c.c.	> 400 c.c.	Variable, with shock
Clinical signs and symptoms	Few	Concealed hem.	Extreme
Prognosis for fetus	Good	Guarded	Poor
Extent of placental involvement	< 1/6	1/6 to 2/3	> 2/3

Table II. Maternal results

Classification	No.	Patients without complications	Patients with morbidity	Patients with anemia	Patients with postpartum hemorrhage
Mild	58	46	5	6	4
Moderate	54	38	6	12	10
Severe	14	7	4	4	3
Total	126	91 (72%)	15 (11.9%)	22 (17.4%)	17 (13.5%)

Table III. Fetal results

	Surviving infants				Perinatal loss					
	Mature		Premature		Absent fetal heart on admission		Intrapartum fetal deaths		Neonatal mortality	
	Vaginal delivery	Cesar- ean section	Vaginal delivery	Cesar- ean section					Vaginal delivery	Cesar- ean section
					Vaginal delivery	Cesarean section	Vaginal delivery	Cesarean section		
14 Severe	—	1	—	—	5	3	2	—	1	2
55 Moderate	14	3	7	4	12	—	11	—	2	2
60 Mild	30	1	16	2	5	1	1	—	4	—
Total (129)	49 (38%)		29 (22%)		26 (20%)		14 (11%)		11 (9%)	

carried out in the operating room with rupture of membranes in 41 cases, and membranes were ruptured in 46 additional cases at examination in the case room. Only 6 patients were given Pitocin in this series. There were 19 cesarean sections: 5 classical, 3 low longitudinal, 6 low transverse, and 5 of the Porro type. Our cesarean section rate is, therefore, 15 per cent. This compares with the 7.8 per cent cesarean section rate in Studdiford and Decker's series.<sup>8</sup> Bysshe<sup>6</sup> quotes a rate of 12 per cent prior to 1950 and one of 30 per cent in recent years. Douglas and associates<sup>7</sup> have a cesarean rate of 40 per cent. In Daro's<sup>1</sup> Cook County Hospital series of 1939 to 1950, the cesarean section rate was 12 per cent, and, in a 1951 to 1953 series, only one case of cesarean section was reported in 104 cases. This last is the low extreme of a complicated picture.

#### Maternal results

Our maternal results compare favorably with any of the above-mentioned series (Table II). There were no maternal deaths.

Only one case of hypofibrinogenemia that required intravenous fibrinogen was diagnosed. There were probably other cases of undiagnosed hypofibrinogenemia as evidenced by 5 Couvelaire uteri and a high percentage of postpartum hemorrhage (17, or 13.5 per cent). Many authors believe both of these phenomena to be due to decreased coagulability of the blood.

There were 15 cases of 11.9 per cent of mild to major degrees of morbidity, the major ones being 2 cases of pneumonia, one of pulmonary embolism, 4 major intra-

uterine infections, one wound infection, and one paralytic ileus. As only a few patients were given prophylactic antibiotics, it is believed that this morbidity might have been reduced by their wider use. Similarly, the high incidence of moderate to severe anemia of 22 patients with a postpartum hemoglobin under 65 per cent suggests that not enough blood has been given early enough.

#### Fetal and neonatal results

There were 129 infants involved in this series of 126 cases (Table III). The gross perinatal mortality rate was 39.5 per cent. Eleven of these deaths involved 6 immature fetuses weighing less than 1,000 grams and 5 major anomalies incompatible with life, resulting in a corrected perinatal mortality rate of 31 per cent. This rate compares favorably with Eastman's<sup>4</sup> statement that "the perinatal mortality is very high and will range between 30 and 60 per cent depending upon the definition of abruptio used." Bysshe<sup>6</sup> believed that the Sloane Hospital reduction of fetal mortality rate from 35 per cent to 23.6 per cent after 1950 is due to the increased cesarean section rate of 30 per cent from the previous rate of 12 per cent. On a careful review of our charts with this point in mind, it appears that, theoretically at least, 5 of the 11 babies who suffered intrapartum fetal deaths during normal but prolonged labor in cases of moderate abruptio placentae might have been salvaged if a cesarean section had been performed within 6 hours. These cases involved 3 full-term primigravidas who were toxic, and 2 multi-gravidas in whom the fetal heart indicated



distress during prolonged labor. It is the opinion of many that, even in those cases where a primary decision to deliver from below has been made, if labor becomes unduly prolonged or the fetal heart begins to show signs of distress, a cesarean section should be performed, especially for those babies whose weight is estimated to be 2,000 grams or more.

### Summary

1. This is an analysis of 126 cases of abruptio placentae, an incidence in our clinic of 0.48 per cent.
2. Antecedent toxemia was present in 11 per cent.
3. Prematurity or immaturity was a factor in 56 per cent.
4. Nineteen cesarean sections were performed, a rate of 15 per cent.
5. There were no maternal deaths, and major complications were minimal.
6. The perinatal mortality rate, corrected

only for immaturity below 1,000 grams and major anomalies, was 31 per cent.

### Conclusions

1. Modern management of abruptio placentae demands immediate blood replacement and repeated observation of the patient's clotting ability.
2. Early rupture of membranes is imperative.
3. The role of cesarean section is controversial. Most observers agree that cesarean section should be performed if delivery is not anticipated within 6 hours in any but the mild cases of abruptio placentae.
4. If the fetal heart shows distress in labor, cesarean section may be lifesaving for the baby. It may have to be performed even with an absent fetal heartbeat, if bleeding is persistent and delivery not imminent.
5. A high incidence of morbidity and moderate to severe anemia suggests need for greater use of prophylactic antibiotics and blood transfusions.

### REFERENCES

1. Daro, A. F., Gollin, H. A., Nora, E. G., Jr., and Primiano, N.: *AM. J. OBST. & GYNEC.* 72: 599, 1956.
2. Bieber, G. F.: *AM. J. OBST. & GYNEC.* 65: 257, 1953.
3. Sexton, L. I., Hertig, A. T., Reid, D. E., Kellogg, F. S., and Patterson, W. S.: *AM. J. OBST. & GYNEC.* 59: 13, 1950.
4. Eastman, N. J.: *Williams' Obstetrics*, ed. 11, New York, 1956, Appleton-Century-Crofts, Inc., chap. 24.
5. Weiner, A. E., Reid, D. E., and Roly, C. C.: *AM. J. OBST. & GYNEC.* 66: 475, 1953.
6. Bysshe, S. M.: *S. Clin. North America* 37: 393, 1957.
7. Douglas, A. G., Buckman, M. I., and Macdonald, F. A.: *J. Obst. & Gynaec. Brit. Emp.* 62: 710, 1955.
8. Studdiford, W. E., and Decker, W. H.: *Obst. & Gynec.* 1: 418, 1953.

# Pelvic tuberculosis

D. NELSON HENDERSON, M.D.

JOHN L. HARKINS, M.D.

JOHN F. STITT, M.D.

*Toronto, Ontario*

THE observations that constitute this paper were made on 69 proved cases of pelvic tuberculosis cared for by a gynecological medical team at the Toronto General Hospital or at the Toronto Hospital for Tuberculosis at Weston. A few cases were gathered from the private service at the Toronto General Hospital. This report is a preliminary survey of a continuing study at these hospitals. This paper will deal largely with the problems of diagnosis and treatment.

Tuberculous pelvic inflammatory disease is not a common gynecological disorder. During recent years, however, because of an influx of large numbers of European immigrants, an increasing number of cases are being encountered each year in Toronto. Because of the alteration that antimicrobial therapy has wrought in the management of this disease, it was considered that a review and report of our cases would be of value.

## Diagnosis

The diagnosis of pelvic tuberculosis is not frequently made on purely clinical grounds. In the material of this study, coming from a wide variety of sources, the diagnosis was entertained in only 10 per cent of the cases prior to curettage or laparotomy.

Forty-eight of the cases were diagnosed by laparotomy and 19 by curettage or endo-

metrial biopsy. In 2 cases the diagnosis was based on clinical demonstration of pelvic masses in patients with active tuberculosis elsewhere.

Our experience has shown that the diagnosis was most often made as a result of laparotomy for pelvic pain or pelvic mass, or in the investigation of the endometrium for infertility or menstrual aberration. However, in retrospect, we believe that the diagnosis would have been made more frequently if greater attention had been paid to certain details of history, examination, and investigation.

**History.** A history of active or quiescent tuberculosis in a patient suffering from pelvic inflammatory disease, infertility or menstrual disturbance should alert the gynecologist to the possibility that tuberculosis may be the etiological agent in the pelvic disorder. In our cases 80 per cent of the patients had evidence of latent or active tuberculosis. This is in agreement with figures quoted by other writers on this subject.<sup>1</sup> The two common presenting complaints were lower abdominal pain and sterility followed in order by disorders of menstruation, abdominal swelling, and leukorrhea (Table I).

**Physical examination.** There are no points in clinical examination that will permit one to make an unqualified diagnosis of pelvic tuberculosis. The presence of a chronic pelvic inflammatory mass in a patient with no history of previous acute pelvic inflammatory disease and with little likelihood of gonococcal infection makes the diagnosis a reasonable possibility.

*From the Department of Obstetrics and Gynaecology, University of Toronto, Toronto General Hospital, and the Toronto Hospital for Tuberculosis, Weston.*

*Presented at the Fifteenth Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, Mont Tremblant, Quebec, Sept. 11-13, 1959.*

**Table I.** Symptomatology in 69 patients with pelvic tuberculosis

Abdominal or pelvic pain	44
Sterility	38
Menstrual disorders	22
Menorrhagia	8
Metrorrhagia	7
Amenorrhea	3
Postmenopausal bleeding	2
Dysmenorrhea	2
Abdominal swelling	13
Leukorrhea	3

**Bacteriological and pathological investigation.** When the diagnosis is suspected on history or physical examination, recourse to menstrual culture<sup>2</sup> or endometrial biopsy are preferred avenues of investigation. Endometrial biopsy may be carried out by the usual method of curettage or by means of a suction curette. The optimal time to examine the endometrium is immediately before the menstrual period. The biopsy material should be sent for pathological and bacteriological examination. Culture of the mycobacterium tuberculosis, in laboratories familiar with the complexities of the method, is very satisfactory and makes guinea pig inoculation rarely necessary.

**Radiological examination.** Hysterosalpingogram may at times be diagnostic although we believe that this is rarely so and it is not without risk to the patient. Stallworthy<sup>3</sup> stated that this form of investigation should not be undertaken until the patient has had tuberculous salpingitis reasonably excluded.

### Pathology

The histological changes encountered in pelvic tuberculosis rarely cause the pathologist difficulty in diagnosis. The fact that the majority of our cases were diagnosed from material obtained at laparotomy emphasizes the importance to the gynecologist of recognizing the gross pathological changes of pelvic tuberculosis. The diagnosis of tuberculous salpingitis at laparotomy is relatively easily made if the classical signs of the lesion are present. Serosal tubercles, thickened tortuous tubes frequently with pouting fimbrial ends, dense adhesions, and

free fluid are typical. Unfortunately, however, in many cases the diagnosis is not so clearly evident and the specific nature of the lesion may not be recognized. When such is the case, more careful inspection may reveal widely scattered discrete tubercles on pelvic peritoneum, omentum, or serosa of the bowel or appendix. Small areas of caseation or calcification between omental adhesions to uterus, tubes, and ovaries may be noted. Biopsy specimens from suspicious areas or from the tubal fimbria for quick section diagnosis may reveal the true nature of the lesion.

### Treatment

**Results.** The treatment of our cases divides them into 3 major categories: (a) drug therapy alone, 38; (b) drug therapy plus operation, 8; (c) inadequate therapy (medical or surgical), 20.

The 3 remaining cases have been treated too recently for the outcome to be evaluated.

In the first category, once diagnosis was established, the patient was admitted to the sanatorium and placed on at least two and usually three of the antituberculosis drugs for a period of 12 to 18 months. Thirty-four of the 38 patients have been followed from 6 months to 4 years after completion of therapy. None of these patients have required further therapy for tuberculosis in the pelvis or elsewhere in the body.

In the second category were 8 patients in whom operation was required after 4 to 18 months of drug therapy. The indication for operation in all 8 cases was a persisting tender pelvic mass. All were treated by bilateral salpingo-oophorectomy and hysterectomy. No serious postoperative complications were encountered. Two patients have been lost to follow-up, and 6 have remained well for from 6 months to 4 years.

The third category contains 20 cases that we consider were inadequately treated. Ten are lost to follow-up, and 3 are alive and well. Of the remaining 7, 2 are dead and 5 have developed recurrence of the pelvic tuberculosis or tuberculosis elsewhere. It is of interest that 2 of the recurrences occurred



when no chemotherapy was given after incomplete operation. One of the patients who received PAS (para-aminosalicylic acid) and streptomycin alone developed meningeal tuberculosis after hysterectomy. Another on this regime had a recurrence after 4 years. One patient treated by radical operation followed by PAS and streptomycin for only 4 months developed renal tuberculosis 2 months after cessation of drugs.

**Sanatorium care.** The antimicrobial treatment of pelvic tuberculosis for the first few months at least should be carried out in a sanatorium. While strict bed rest is no longer necessary, the patient will derive much benefit from the environment of the sanatorium, being educated in regard to the serious nature of the disease and impressed with the necessity of long-term drug therapy. The frequency of drug reactions during the first 3 months of therapy requires careful observation of the patient, desensitization techniques, and changes in the drugs used, all of which can be best managed in a sanatorium.

**Drug therapy.** The 3 important drugs used in the treatment of tuberculosis are isoniazid, streptomycin, and para-aminosalicylic acid (PAS). These 3 should be given in combination of 2 or 3 drugs concurrently in order to delay the emergence of drug-resistant forms of tubercle bacilli within the tuberculous lesion. Streptomycin is given in dosage of 1 Gm. twice weekly, isoniazid, 300 mg. daily, and PAS, 14 Gm. daily. When streptomycin is used with isoniazid alone, the dose should be 1 Gm. daily. Isoniazid is the most effective of these agents because of its excellent penetrating properties and high bacteriostatic activity; it is followed by streptomycin. PAS owes its place in the combination to its ability to delay the emergence of organisms resistant to streptomycin. Our early experience with drug therapy in tuberculosis generally and our small experience with streptomycin and PAS as the only forms of chemotherapy highlight the fact that isoniazid appears to be the essential drug in the combination of drugs used in treating this disease.

Drug toxicity is a problem in approximately 10 per cent of patients receiving all 3 drugs. Many of the manifestations of drug toxicity are of a minor nature and are readily controlled, but more serious reactions, such as purpura, hepatitis, and encephalitis, may result from PAS toxicity; eighth nerve damage from streptomycin; and severe peripheral neuritis or acute psychosis from isoniazid.

The treatment of all forms of tuberculosis is essentially the same as far as chemotherapy is concerned, necessitating a combination of two or more antibiotics provided isoniazid is included. Most forms of extrapulmonary tuberculosis are hematogenous in origin and, therefore, may be associated with quiescent or frankly active lesions elsewhere. Failure to realize this may result in inadequate treatment if all therapy is directed to the removal of the obvious lesion.

Our experience with drug therapy in the past 7 years in the treatment of all forms of tuberculosis has shown that the drugs must be administered without significant interruption for a minimum period of one year and preferably for 18 months.

**Surgical therapy.** If tuberculous pelvic inflammatory disease is unexpectedly encountered at laparotomy, the abdomen should be closed after biopsy specimens have been taken to establish an unequivocal diagnosis. If the disease is extensive, operation is difficult and the risk of injury to the bowel with resulting fistula is considerable. In 25 cases treated surgically at the Toronto General Hospital before 1940, there were 2 bowel fistulas and 2 deaths, one from miliary tuberculosis and one from intestinal obstruction. TenBerge<sup>4</sup> reported 21 surgically treated cases before drug therapy with 2 deaths and 3 fistulas and compared them with 19 cases operated upon after drug therapy with no deaths and one fistula. Subsequent operation may never be required, but, if it does become necessary, the risk of serious complications is lessened and less radical operation than total hysterectomy and bilateral salpingo-oophorectomy may be adequate.

The indications for operation in the patient who has received adequate drug therapy will vary to some extent according to the age, parity, and emotional status of the patient. The presence of a persistent large adnexal mass (particularly if tender), persistent or recurrent pelvic pain, menorrhagia, or bowel fistula warrants surgical intervention. The extent of the operation in such cases will be determined by the indications for operation and the degree of resolution of the inflammatory masses which has resulted from drug therapy. While in the past the surgical treatment of choice has been bilateral salpingo-oophorectomy and hysterectomy, it would now seem reasonable to consider less radical surgical treatment. The majority of these patients are young women and, while there is only faint hope for future pregnancy, the preservation of that hope along with ovarian function and menstruation is often of great psychological importance. Time alone will establish whether such conservative surgical treatment is justified in the medically treated case of tuberculous pelvic inflammatory disease.

#### Summary

The cases reviewed in this presentation have served to emphasize that pelvic tuber-

culosis is a local manifestation of a generalized disease. Failure to realize this and direct therapy to the removal of the obvious pelvic lesion will result in serious complications and treatment failures.

The diagnosis of the lesion is difficult and, unfortunately, is most frequently made at laparotomy. An awareness of the increasing incidence of the disease, its importance as a cause of sterility, and the significance of a history suggestive or positive of past tuberculous infection in a case of pelvic inflammatory disease will lead to a correct diagnosis which might otherwise be missed. In suspected cases, endometrial biopsy, curettage, and culture may establish a positive diagnosis.

Once the diagnosis is established, the patient should receive the initial treatment under sanatorium conditions. The results with antimicrobial therapy with use of two and usually three of the antituberculosis drugs, justify the place of medical therapy as opposed to surgical extirpation of the pelvic organs. If adequately treated medically, less than 20 per cent of the cases will require operation, and should operation be deemed necessary it may be of limited extent and carried out with greater safety to the patient.

---

#### REFERENCES

1. Barns, Tom: J. Obst. & Gynaec. Brit. Emp. 62: 162, 1955.
2. Halbrecht, I.: J. A. M. A. 142: 33, 1950.
3. Stallworthy, J. A.: Postgrad. M. J. 32: 517, 1956.
4. TenBerge, B. S.: Arch. Gynäk. 186: 310, 1955.

# Culdoscopy

ALBERT B. BROWN, M.D.

KEITH M. CROCKER, M.D.

*Saskatoon, Saskatchewan*

NEW diagnostic aids are steadily being introduced to make the practice of medicine a more exacting science. To be of great value, a diagnostic tool must be simple to operate, have a high degree of accuracy, and cause a minimum of complications. Our present technique of culdoscopy was introduced by Decker and Cherry<sup>1</sup> in 1944 and has measured up to these requirements. Many clinics have adopted this valuable diagnostic procedure but there are still centers where culdoscopy is virtually unknown.

This paper is based on a study of culdoscopy at the new University Hospital in Saskatoon from March, 1955, to March, 1959. Until 1955, when culdoscopy was introduced to the gynecological service by one of us (A.B.B.), none of the other gynecologists had used the culdoscope, and consequently our results include a considerable number of cases managed by inexperienced operators.

The popularity of the diagnostic procedure is well demonstrated by the fact that in the 4 year period, 8 operators carried out a total of 205 culdoscopies on 203 patients, two of the patients having repeat examinations. We believe that previous culdoscopy is not a contraindication to further culdoscopic examinations.

## Anesthesia

Some authors<sup>2</sup> prefer the use of local anesthesia for culdoscopy. In our clinic, how-

ever, all patients receive a general anesthetic for such an examination. This is done partly to avoid discomfort to the patient but also because many of the procedures are combined with dilatation and curettage. The anesthetic agent employed in the vast majority of cases is Pentothal Sodium. As has been stressed by Josey and associates,<sup>3</sup> with the anesthetized patient in the knee-chest position intratracheal intubation is an absolute necessity. Failure to do this may result in anoxia. A pillow placed under the chest is also a help in straightening the airway.

## Technique

The patient is anesthetized, an intratracheal tube is inserted, and she is placed in the dorsal lithotomy position for a pelvic examination under anesthesia. This is most important for two reasons. First, it may reveal unsuspected abnormalities of the pelvis, and, second, unless the vaginal and abdominal fingers meet behind the cervix, indicating that the pouch of Douglas is free, culdoscopy should not be attempted. The patient is then placed in the knee-chest position and a pillow inserted under the chest. Braces are fixed above the shoulders to prevent the patient from sliding forward. Several authors<sup>4, 5</sup> have described apparatuses for maintaining the anesthetized patient in the knee-chest position. We accomplish this by strapping the thighs to padded supports attached to the sides of the operating table. The patient is then prepared as for any vaginal operation; she is draped and the culdoscope introduced through a puncture wound in the posterior fornix.

Visualization of the pelvic organs may be facilitated in many cases by manipulation of

*From the Department of Obstetrics and Gynaecology, University of Saskatchewan, and The University Hospital.*

*Presented at the Fifteenth Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, Mont Tremblant, Quebec, Sept. 11-13, 1959.*



**Table I.** Age distribution of patients examined by culdoscopy

<i>Age group</i>	<i>No. of cases</i>
10-19	4
20-29	104
30-39	75
40-49	19
50-54	3
Total	205

**Table II.** Indications for culdoscopy

Unexplained abdominal or pelvic pain	71
To establish the diagnosis of endometriosis	37
As part of endocrinological investigation	33
To establish ectopic pregnancy	29
To establish pelvic inflammatory disease	20
To determine the nature of pelvic masses	8
As part of the investigation for infertility	7
Total	205

the anterior abdominal wall. If the intestines do not seem to fall away from the pelvic organs, this may be accomplished by traction on the anterior abdominal wall, which will increase the pneumoperitoneum. When the culdoscope is about to be removed, air should be expressed from the abdominal cavity; this reduces the postoperative discomfort.

#### Age of patients

It will be noted from Table I that the culdoscope is of most value in the investigation of patients who are in the childbearing years. This can perhaps be accounted for by the fact that ectopic pregnancy, endometriosis, and pelvic inflammatory disease are almost entirely confined to the reproductive period of life. In our series, the ages varied from 12 to 54 with an average of 30.

#### Indications

As will be noted from Table II, the most common indication for culdoscopy in our clinic is unexplained abdominal or pelvic pain. The culdoscope is also frequently used to rule out or establish the diagnosis of ectopic pregnancy or pelvic inflammatory disease and as a part of an endocrinological investigation. Its use, however, is somewhat

infrequent in the investigation of infertility or the nature of pelvic masses.

**Pelvic pain.** In our clinic the culdoscope has proved to be of most value in those patients who complain of pelvic or lower abdominal pain for which no obvious cause can be found. This is perhaps explained by the fact that we are a university center with a high referral rate for this type of patient and in many such cases a laparotomy was prevented.

Seventy-one of our cases fell into this group. Of these, 49 were found to have normal internal genitals. As far as is known, only 2 of these patients subsequently came to laparotomy and in both cases the culdoscopic findings were confirmed.

Endometriosis was diagnosed in 6 of the cases with only 2 of these considered severe enough to warrant laparotomy, and in both cases the diagnosis of endometriosis was proved to be incorrect. In one case, varicose veins of the broad ligament were wrongly interpreted as endometriosis, while in the second a blood-filled corpus luteum was thought to be a chocolate cyst.

Pelvic inflammatory disease was diagnosed in 6 cases and as far as is known none of these have come to abdominal exploration.

In 3 cases either a corpus luteum or a corpus luteum cyst was found on culdoscopic examination. In one of these, although there was some bleeding from the corpus luteum, it appeared to have stopped and no further treatment was considered necessary. In a second case, a ruptured corpus luteum was found to be actively bleeding. Abdominal exploration confirmed the diagnosis, and the rent was repaired. The third was a case of a corpus luteum cyst which was diagnosed by the culdoscopist but because of poor visualization a laparotomy was undertaken. Because this latter procedure was necessary to confirm the diagnosis, this culdoscopic examination is classified as unsatisfactory.

In 4 cases, varicose veins were found on culdoscopic examination. Only one of these came to abdominal exploration, and the diagnosis proved to be correct. Leiomyomas

of the uteri were found in 2 cases but, because they were small, an operation was not performed. In only one case was the culdoscopist unable to introduce the scope into the peritoneal cavity.

Laparotomy was performed in 7 cases. Culdoscopy was unsuccessful in 2 cases (2.9 per cent); an incorrect diagnosis was given in 2 cases (2.9 per cent).

**Endometriosis.** It is well known that endometriosis is not found in all patients who give a history characteristic of the lesion. In our series, the diagnosis on admission was endometriosis in 37 cases. At the time of culdoscopy the lesion was proved to exist in only 9. Only 2 of these patients required abdominal operation and in both endometriosis was proved on pathological study of the tissue removed. As far as is known, no cases of endometriosis were missed on culdoscopy.

**Endocrinological investigation.** With the increasing knowledge of hormonal disorders it has become of great assistance to visualize the internal genitals as part of some endocrinological investigations. This is particularly true of such conditions as the Stein-Leventhal syndrome or where small functioning ovarian tumors are suspected.

Thirty-three of our patients were examined with the culdoscopy as part of their endocrinological investigation. Of these 25 were found to have normal internal genitals, 7 had ovaries typical of the Stein-Leventhal syndrome and one patient was found to have hypoplastic ovaries. Six of the 7 patients with Stein-Leventhal syndrome have had wedge resections of the ovaries with confirmation of the culdoscopic diagnosis in every case. In addition there was one instance where the culdoscopist called the ovaries normal but at subsequent laparotomy the diagnosis of Stein-Leventhal syndrome was proved.

**Ectopic pregnancy.** If hemoperitoneum or a pelvic mass exists, the diagnosis of tubal pregnancy may be relatively simple. Often, however, there is a good deal of doubt about the diagnosis. It is in these difficult cases that the culdoscope has been of great value.

Twenty-nine of our cases were of the latter type. On culdoscopic examination 9 were thought to be tubal pregnancies for which abdominal operation was carried out. The diagnosis was incorrect in 3 of the cases. The incorrect diagnoses were the result of misinterpretation of varicose veins of the broad ligament, a corpus luteum, and a hydrosalpinx. In no case was an ectopic pregnancy missed by the culdoscope.

**Pelvic inflammatory disease.** Patients who have marked pelvic inflammatory disease are not suitable candidates for culdoscopy because the pouch of Douglas is often obliterated by adhesions. However, in these cases the diagnosis is usually obvious, and they may require pelvic operation. The cases of P.I.D. in which the culdoscope is of most value are those in which the history is suggestive of chronic P.I.D. but in which the pelvis is found to be normal or almost normal on bimanual examination.

Twenty of our patients were admitted with the provisional diagnosis of pelvic inflammatory disease. The diagnosis was confirmed by culdoscopy in 10 and, of the remainder, 8 were thought to have normal pelves, one was found to have a retention cyst of the ovary, and in one case the examination was unsatisfactory because of a defective lens. Three of the 10 patients diagnosed as having P.I.D. had subsequent pelvic operation at which time the diagnosis was confirmed in each case. In one case where the pelvis was called normal on culdoscopic examination subsequent abdominal operation revealed adenomyosis and a small myoma on the anterior surface of the uterus, both conditions being undiagnosable by culdoscopy; however, this is classified as a case of error in diagnosis. There was one unsatisfactory culdoscopy in this group (5%).

**Pelvic masses.** One would expect the culdoscope to have its greatest use in determining the nature of pelvic masses. Unfortunately, this is not true because, first of all, if the mass fills the cul-de-sac this obviates the possibility of culdoscopy. Second, in the case of large masses, even if the culdoscope can be introduced, because of magnification

and the closeness of the lens to the mass it is often difficult to identify the nature of the mass. We feel that if there is a tumor in the pelvis abdominal exploration is not only more accurate in making the diagnosis but is often the indicated method of management. However, there are a few cases where a small ovarian tumor, functioning or otherwise, is suspected, in which case the culdoscope may be helpful.

In 8 of our cases the provisional diagnosis was ovarian cyst. In 3 of these the culdoscopist diagnosed a corpus luteum. In 2 others the cyst proved to be of the follicular type. One patient, aged 12, had a history of precocious puberty and menorrhagia since the age of 9. A small granulosa or theca cell tumor was suspected, but culdoscopy demonstrated normal ovaries. Of the remaining two cases one was diagnosed as P.I.D. with adhesions between the intestine and the right adnexa and the other was considered to be a normal large ovary. In no case was the diagnosis proved wrong.

**Infertility.** We have found that culdoscopy is of limited value in the investigation of infertility. However, there are cases where it can be of great value—for example, if on hysterosalpingography the tubes are found to be blocked at their uterine ends and one is desirous of knowing the extent of previous pelvic operation or the condition of the proximal portion of the tubes. Only 7 of the patients were examined by means of the culdoscope as part of an infertility investigation.

#### Unsuccessful culdoscopy

Our interpretation of the term "unsuccessful culdoscopy" is that for some reason the pelvic organs could not be satisfactorily visualized. There were 6 (2.9 per cent) unsuccessful culdoscopic examinations in our series. Three of these were due to inability to pass the scope into the pouch of Douglas. In a fourth case there was fogging of the lens for some unknown reason. In spite of this, the diagnosis of a corpus luteum cyst was made, and at laparotomy this was confirmed. However, because pelvic operation

**Table III.** Frequency of unsuccessful culdoscopy in reported series

Author	No. of cases	Unsuccessful	
		No.	%
Abarbanel <sup>2</sup>	400	18	4.5
Brown and Crocker	205	6	2.9
Josey, Thompson, and TeLinde <sup>3</sup>	594	45	7.6
Kelly and Rock <sup>6</sup>	492	75	15.2
Noyes <sup>7</sup>	130	21	16.2
Riva et al. <sup>8</sup>	1,500	59	3.9
Clyman <sup>9</sup>	960	39	4.1
Green <sup>10</sup>	150	7	4.7
Total	4,431	270	6.1

was necessary to establish the diagnosis, this is considered an unsuccessful case. The fifth case was unsuccessful because of a broken lens in the culdoscope, and the final case was considered unsuccessful because the intestine obscured the view of the right ovary which was thought to be the site of endometriosis.

In our center it would appear that successful culdoscopy can be carried out on 95 per cent of the cases attempted. This is only possible if there is a careful selection of cases. In Table III, the rate of unsuccessful culdoscopy in this and 7 other large series of cases, which includes over 4,000 culdoscopic examinations, is summarized. The over-all incidence of failure was 6.1 per cent.

#### Complications

Only 2 (1 per cent) patients developed complications as a result of culdoscopy. In one the operator was unable to introduce the scope. Subsequent laparotomy showed this to be due to the fact that the intestine was adherent to the posterior aspect of the uterus. Careful study of the bowel failed to demonstrate any perforation, although emphysema and a hematoma were found under the serosa. The patient had an uneventful postoperative course. Usually, if there is extraperitoneal perforation of the bowel, no active treatment is necessary. If there is transperitoneal perforation of the intestine, the puncture wound should be closed.

The second complication was a single case of postoperative vaginal bleeding that oc-



curred 6 days following culdoscopy. Examination showed the site of the hemorrhage to be the culdoscopy puncture wound of the vagina. This was treated by suturing.

#### **Incorrect diagnosis**

It will be noted that the culdoscopist was not always right in his diagnosis. As with any operation, the experienced operator is much more accurate in his interpretation of the findings, and it is obvious that some of our mistakes were due to inexperience on the part of the culdoscopist. However, even the most experienced will make an occasional incorrect diagnosis.

In our series of 199 culdoscopies (excluding the unsatisfactory operations) there were 7 (3.5 per cent) incorrect diagnoses made. Of the 7 cases, only one was diagnosed as a normal pelvis on culdoscopy and later found to be the site of a pathological lesion. Thus, it would appear that there is a greater tendency to overdiagnose rather than underdiagnose.

#### **Laparotomies**

It would appear that laparotomy was avoided in many of the cases. Of the 205

cases only 28 were followed by abdominal operation.

It would appear that previous pelvic operation or appendectomy is not a contraindication to culdoscopy. In our series, 94 of the patients gave a history of having had an appendectomy and 37 of having had pelvic operations. In none of these cases were there any complications attributable to adhesions resulting from the previous operation.

#### **Summary**

A study of 205 culdoscopic examinations carried out on 203 patients has been presented. We believe that the culdoscope has proved to be a very worthwhile diagnostic aid to the gynecologist. It is of most use in patients complaining of unexplained abdominal or pelvic pain but also is a help in the investigation of patients suspected of having endometriosis, ectopic pregnancy, pelvic inflammatory disease, or some endocrinological disorder. The instrument is only occasionally of value in the investigation of pelvic masses or infertility. To our gynecological staff the culdoscope has taken a place of value almost comparable to the urologist's cystoscope.

---

#### **REFERENCES**

1. Decker, A., and Cherry, T. H.: *Am. J. Surg.* 64: 40, 1944.
2. Abarbanel, A. R.: *Am. J. Surg.* 90: 122, 1955.
3. Josey, W. E., Thompson, J. D., and TeLinde, R. W.: *South. M. J.* 50: 713, 1957.
4. Blair, L. C.: *Surg. Gynec. & Obst.* 96: 249, 1953.
5. Brown, A. B., and Bear, S. A.: *AM. J. OBST. & GYNEC.* 66: 912, 1953.
6. Kelly, J. V. and Rock, J.: *AM. J. OBST. & GYNEC.* 72: 523, 1956.
7. Noyes, R. W.: *Obst. & Gynec.* 3: 314, 1954.
8. Riva, H. L., Hatch, R. P., and Breen, J. L.: *Obst. & Gynec.* 12: 610, 1956.
9. Clyman, M. J.: *S. Clin. North America* 37: 1357, 1957.
10. Green, J. H.: *New England J. Med.* 254: 214, 1956.

# Further observations on a simple procedure to eliminate thrush from hospital nurseries

L. J. HARRIS, M.D., M.A., F.R.C.S.(C.)

Toronto, Ontario

THRUSH or oral candidiasis is a common condition found in nurseries for the newborn all over the world. It is caused by a fungus known as *Candida* or *Monilia albicans* which is also found in the vaginas of adult women. According to published statistics from various centers it occurs in about 4 per cent of all newborn infants in the first week of life.<sup>1-4</sup> All studies show a high correlation between the appearance of thrush in the infant and the presence of *C. albicans* in the vagina of the mother, so that there is presumptive evidence that the disease may be contracted from the mother during birth.<sup>4-9</sup> However, there is no doubt that it can be transferred by personnel handling the babies or by improperly sterilized bottles or nipples,<sup>10</sup> as is evidenced by the not infrequent outbreaks of epidemics in nurseries.<sup>11</sup>

The disease is usually mild and limited to the appearance of white patches in the mucous membrane of the mouth and throat, but it not infrequently spreads to the gastrointestinal tract and perianal region and occasionally to the trachea, bronchi, and lungs, leading to serious illness and at times even death.<sup>10, 12</sup> At the very least it is a source of considerable annoyance to hospitals, doctors, and patients and almost always is taken by the mother as evidence of poor nursing or physician care.

It thus tends to reflect discredit on the hospital and the physician while at the same

time it imposes the need for extra care, treatment, and isolation of the infants concerned.

## Purpose of investigation

A simple, safe, and inexpensive procedure that would completely eradicate thrush from hospital nurseries would prove to be almost, if not equally, as great a boon as the eradication of ophthalmia neonatorum by the use of silver nitrate.

With this in view, in 1957, the Departments of Obstetrics, Pediatrics, and Bacteriology at The New Mount Sinai Hospital in Toronto undertook a very complete controlled study to determine the facts about the source, transmission, and incidence of *C. albicans* infections in infants, and to see if this condition could be eradicated by instilling a nystatin\* suspension into the mouths of newborn infants.

## Technique and results

A total of 4,243 infants were investigated. In the first series 1,500 consecutive newborn babies were studied. Repeated cultures and smears were taken from the mothers' vaginas before and after delivery and also at intervals from the infants' mouths. The infants were placed alternately in two groups. Those in Group A were given an instillation of 1 c.c. or 100,000 units of nystatin in suspension, by means of an eyedropper into the oral cavity daily. Because nystatin is only slightly soluble, it is essential that the solution be

*From the New Mount Sinai Hospital.*

*Presented at the Fifteenth Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, Mont Tremblant, Quebec, Sept. 11-13, 1959.*

\*Supplied as Mycostatin, an antifungal antibiotic, by E. R. Squibb & Sons of Canada, Ltd.

shaken vigorously before it is instilled. Those in Group B served as controls and were not given any treatment.

It is not our intention to go into all the conclusions that were reached regarding the types of organisms, sources of infection, methods of transmission, and relationship to type of labor and antepartum conditions in the mother, except to say that many interesting facts were elicited which can be found in our original article.<sup>4</sup>

**Results with daily instillations.** We would like to emphasize, however, that of the 750 infants treated as described with nystatin, not one developed thrush in the hospital and only 3 developed it within one week after discharge—whereas among the controls there were 31 cases of thrush—an incidence of 4 per cent. These findings are highly significant in that the possibility of their occurring by chance is less than 1 in 1,000.

A total of 933 infants were treated with daily instillations of nystatin and not one developed thrush in the hospital.

**Results with two instillations.** The number of instillations was then reduced so that the babies received only one on the second and one on the fifth day of life. In this series there were 1,000 consecutive babies without a single case of thrush.

**Results with one instillation.** Following this the instillations were further reduced to only one given on the third day of life. In this series of 1,560 babies treated with one instillation, 4 developed thrush: 1 was a critically ill baby, 2 were weak premature

infants, and 1 was an apparently normal child.

### Other findings

**Cost.** The cost of this medication to the hospital is less than 5 cents per child, and it is very simple to administer.

**Toxicity.** There have been no side effects or complications from this treatment.

**Resistant strains.** We have not noted the development of any resistant strains of *C. albicans* in our series, and repeated attempts to produce resistant strains of this organism in the laboratory have also failed.

**Present procedure.** We are now instilling with an eyedropper, after shaking well, 100,000 units of the suspension into the mouths of all infants on the second and the fifth day of life, and we feel reasonably confident that there will be no further thrush in our nurseries. The effect of this on the nursing staff and doctors has been most gratifying.

### Conclusions

One instillation of nystatin on the third day of life reduces the incidence of oral candidiasis in infants from 4 to 0.4 per cent.

Two instillations of nystatin, one on the second day and one on the fifth day of life, given properly will prevent thrush in 100 per cent of all hospital babies.

It is strongly recommended that all hospitals adopt this simple, inexpensive, and harmless procedure in order to completely eradicate thrush as a nursery problem.

### REFERENCES

1. Taschdjian, C. L., and Kozinn, P. J.: *J. Pediat.* 50: 426, 1957.
2. Woodruff, P. W., and Hesselstine, H. C.: *AM. J. OBST. & GYNEC.* 36: 467, 1938.
3. Shardt, A., and Roy, T. E.: *Canad. M. A. J.* 76: 1029, 1957.
4. Harris, L. J., et al.: *Canad. M. A. J.* 79: 891, 1958.
5. Plass, E. D., Hesselstine, H. C., and Borts, I. H.: *AM. J. OBST. & GYNEC.* 21: 320, 1931.
6. Carter, B., and Jones, C. P.: *South. M. J.* 30: 298, 1937.
7. Weinstein, L., and Wickerham, L. J.: *Yale J. Biol. & Med.* 10: 553, 1938.
8. Hesselstine, H. C., Borts, I. C., and Plass, E. D.: *AM. J. OBST. & GYNEC.* 27: 112, 1934.
9. Bland, P. B., Rakoff, A. E., and Pincus, I. J.: *Arch. Dermat. & Syph.* 36: 760, 1937.
10. Ludlam, G. B., and Henderson, J. L.: *Lancet* 1: 64, 1957.
11. Anderson, N. A., Sage, D. N., and Spaulding, E. H.: *Am. J. Dis. Child.* 67: 450, 1944.
12. Lederer, H. and Todd, R. M.: *Arch. Dis. Childhood* 24: 200, 1949.



# The value and danger of exogenous oxytocin in obstetrics

C. LEE BUXTON, M.D.

RICHARD HAUSKNECHT, M.D.

*New Haven, Connecticut*

IN THE *Canadian Medical Association Journal* in September, 1913, B. P. Watson,<sup>1</sup> then Professor of Obstetrics and Gynecology at the University of Toronto, published a definitive review of the use of posterior pituitary extract in obstetrics and discussed a number of cases of his own in which he had used this substance for the induction of labor.

Apparently Blair-Bell<sup>2</sup> in 1909 was the first obstetrician to use posterior pituitary extract clinically. He reported 3 cases of postpartum hemorrhage in which the substance was administered effectively and apparently to a greater advantage than the then commonly used ergot preparations. Although posterior pituitary extract was experimented with clinically on frequent occasions subsequent to that time and although it had occasionally been used in an attempt to induce labor, the substance was generally considered to be so potentially dangerous that most conservative obstetricians expressed apprehension concerning its employment, especially for induction or during the first and second stages of labor.

Therefore, it was for the most part not until Watson's report from Toronto that very serious consideration was given to the potentialities of this substance as an inducer

of labor, and, in subsequent publications on both sides of the Atlantic, the technique of multiple intramuscular injections of pituitary extract to induce labor generally became known as "Watson's technique."

From that time on, there were many clinical reports both pro and con concerning this method. Variations in technique of administration were published, including the intranasal application of pledgets with pituitary extract by Hofbauer and Hoerner.<sup>3</sup>

In 1920 Watson<sup>4</sup> read a further report at a meeting of the American Gynecological Society concerning the results in a number of subsequent cases. The paper itself and especially the subsequent discussion gave ample evidence of the enthusiasms and apprehensions at this time concerning this substance—enthusiasms and apprehensions which exist to the present day.

This is not unreasonable because it may well be said that many of the most useful drugs in the pharmacopeia are at the same time the most dangerous, and oxytocin is one of the best examples of this beneficial yet lethal characteristic. As Reid<sup>5</sup> has said in connection with posterior pituitary extract, "To condemn a drug purely because it is not used properly is an unscientific approach."

The potentialities of this drug for pre-delivery use were such that during the next decade it was wisely administered by those who knew of its potential dangers but unquestionably badly abused by many. As a consequence, it was thoroughly condemned by many obstetrical authorities at that time. Eastman<sup>6</sup> expressed it well when he stated

*From the Department of Obstetrics and Gynecology, Yale University School of Medicine.*

*Presented at the Fifteenth Annual Meeting of the Society of Obstetricians and Gynaecologists of Canada, Mont Tremblant, Quebec, Sept. 11-13, 1959.*

"The dangers of pituitary extract in the first and second stages of labor in the form of uterine rupture and fetal asphyxia have been repeatedly and vehemently emphasized and, in the opinion of many authorities, are so menacing that this agent should never be used before the birth of the baby." Hofbauer<sup>3</sup> had effectively used pituitary extract in the control of postpartum hemorrhage and uterine atony in the third stage and, being of the opinion that it had great potentialities in the treatment of intrapartum uterine inertia, he devised the nasal pledget administration technique to control the amount of pituitary extract absorbed by the patient. This was not entirely satisfactory, however, because it was somewhat difficult to tell exactly how much of the material was absorbed through the mucous membrane, and Eastman, for instance, speaks of 2 cases brought to his attention in Baltimore of ruptured uterus following intranasal Pituitrin.

In 1935 the use of this oxytocin in the first and second stages of pregnancy was given up, not only in Baltimore but in many other places in America. Quigley,<sup>7</sup> in Rochester, New York, after publishing a paper recommending the use of pituitary extract in 1915, stated that by 1925 he regretted the fact that the paper had been published because he had seen so much subsequent damage caused by its use.

Many similar comments may be found in the literature during the two decades between 1920 and 1940. The problem of intrapartum uterine inertia, prolonged desultory labor with its high fetal mortality and maternal morbidity, plus the mediocre success in the induction of labor with castor oil and quinine prompted various obstetricians to continue with cautious experimentation. In all probability the reports in 1945 by Reid<sup>5</sup> on 1,500 cases from the Boston Lying-in Hospital and by Eastman<sup>6</sup> in 1946 did much in the United States, anyway, to remove the anathema from this potentially useful drug. Administering pituitary extract with great caution, they confirmed previous impressions that it was possible to use this

hormone safely and, in appropriate cases, to great advantage.

Troubles with the intramuscular technique of administration of pituitary extract continued to be fairly common, however, and in 1948 Theobald and co-workers<sup>8</sup> published their experiences with an intravenous technique using a 1:5,000 dilution, proceeding on the philosophy that parturition occurred as a result of sensitivity of uterine muscle to circulating oxytocin. It seemed only reasonable that if minute amounts of exogenous oxytocin could be put into the blood stream in a continuous process, an appropriately sensitized uterus should respond to it.

In terms of experience over the last 11 years since the publication of this paper, Theobald's<sup>9</sup> indications for induction of labor by this technique have not changed. They were listed as follows: cephalopelvic disproportion, previous cesarean section or difficult labor, toxemia, postmaturity, hydramnios, and placenta previa. Theobald's explanation is that if the hormone is used in "physiological amounts" and not as a "pharmacological substance in weak dilution," it is logical to use oxytocin in any case in which the obstetrician deems labor justifiable. Using the Pitocin drip in over 1,000 cases, starting with a concentration of 1:5,000, he found no untoward alterations in the rhythm or rate of the fetal heart; nor has there been any anxiety concerning the mother. There were no maternal deaths in his series and the fetal mortality rate was about the same as might be expected in patients who had had no induction. Theobald attributes one fetal death to the Pitocin drip in a case where it was incorrectly used.

In spite of the intravenous introduction of this hormone in "physiological amounts," however, whoever administers the solution is cautioned to start the flow rate at no greater than 40 drops per minute and to stay with the patient for at least 30 minutes to be sure that the drip causes no change in the rate frequency or force of the fetal heart, or that uterine contractions do not occur too frequently or become tetanic. In case this occurs, a suggestion is made that a

1:10,000 instead of a 1:5,000 solution be used.

A 1:5,000 solution running at 40 drops per minute delivers 5 mU. of Pitocin per minute to the patient. A solution commonly used in the United States of 1 c.c. or 10 units of Pitocin per 1,000 c.c. of 5 per cent glucose is usually administered to the patient, starting a drip at about 8 drops per minute. This delivers the same number of milliunits per minute as the more dilute solution running at 40 drops. The more dilute solution has the advantage that the speed of administration can probably be measured a little more accurately. The more concentrated solution has the advantage that, should the drip be continued a fairly long while or its speed increased, it is not necessary to administer to the patient quite as much intravenous diluent.

Therefore, in subsequent paragraphs, in which our experiences with intravenous Pitocin are discussed, it may be assumed that the concentration administered to the patient is about the same as that which was used in Theobald's<sup>9</sup> series published in 1956.

Although the pressor and antidiuretic effect of posterior pituitary extract had for a considerable time been separated from oxytocin, the purity of the oxytocic product was verified in 1952 when DuVigneaud and his group<sup>10</sup> crystallized and then synthesized the oxytocic hormone of the posterior pituitary. Subsequent trials with the synthesized oxytocin and the purified oxytocic extract of the posterior pituitary have disclosed no perceptible difference in their physiological and pharmacological activity and either one appears to be quite satisfactory for use when a pure oxytocin is desired.

Since that time the use of Pitocin for induction of labor and for uterine inertia has become fairly standard. It is probable that the concentration of Pitocin administered for the induction of labor is not infrequently too high. One of us (C. L. B.) was somewhat startled to find, when examining candidates for the American Board of Obstetrics and Gynecology, that it was routine in certain parts of the United States to start a Pitocin

induction in a concentration of 1:500 at 20 or 30 drops a minute. It would seem almost inevitable that this would not infrequently produce tetanic contractions and fetal distress.

In order to more closely ascertain the effect of an oxytocic agent on the fetal heart rate, Hess and Hon,<sup>11</sup> of the Department of Obstetrics and Gynecology of the Yale Medical School, carried out a series of fetal electrocardiographic determinations on patients in whom labor was induced by oxytocin. As has been mentioned before, the technique of intravenous administration of oxytocin at Yale is to use a 1:1,000 solution starting at 8 drops per minute and gradually increasing it until uterine contractions ensue, but not longer than a period of 4 hours. If no uterine contractions occur even after an increase of the speed of the intravenous drip to 25 or 30 drops a minute, the induction is then discontinued and the attempt at induction repeated the next day unless normal labor subsequently ensues, which is, incidentally, a fairly frequent event.

The objective findings of the fetal electrocardiograph confirmed the impressions of previous clinical observations that only minor deviations in the fetal heart rate were noted during a routine induction of labor with oxytocin. These minor deviations were considered similar to those encountered in "normal" labor. Fetal electrocardiogram on one patient, in whom the uterine sensitivity was such that a "tetanic" uterine contraction of 5 minutes occurred at the onset of a Pitocin infusion, showed profound bradycardia followed by fetal tachycardia, but fortunately without untoward results. Uterine hypertonus appeared to have a marked effect on fetal heart rate even though the amplitude of the individual contractions was less than average. In a study of 40 labors induced by oxytocin, there was no question but that abnormal deviations in fetal heart rate were noted if the induction was too rapid, and it definitely confirmed the clinical impression that the use of oxytocin intravenously should be carefully supervised, especially at the onset of the infusion as it



may be potentially capable of interfering with fetal oxygenation, particularly under circumstances where fetal circulatory reserve may be compromised by maternal age, eclampsia, maternal hypotension, and perhaps postmaturity.

With these advantages and disadvantages of intravenous oxytocin in mind, this hormone has been used cautiously but with gradually increasing frequency on the obstetrical service at Yale for the last 8 or 9 years.

For the last 5 years the routine for induction of labor or use for uterine inertia during the first or second stages of labor is as previously described. Constant close attendance by the obstetrician is a strict requirement and, on all ward cases, consultation with the attending obstetrician must be obtained before the administration of oxytocin.

In order to adequately review the type of cases in which oxytocin is used on the Yale Service and the results of its use, patients in the years 1957 and 1958 were taken as examples. During these 2 years 2,579 ward patients and 7,329 private patients were delivered at the Grace-New Haven Hospital. In 1957, labor was induced in 52 patients on the ward service or 4.1 per cent of the total deliveries for that year and, in 1958, 100 or 7.5 per cent of the total. The figures for the private service during these 2 years were as follows: 1957, 182 inductions or 4.8 per cent, and 1958, 207 inductions or 5.7 per cent.

Table I gives some indication of the success of these inductions on the ward and private service during these 2 years. Table II presents, in generalities, the results of induced labors. Table III provides some information concerning the usually accepted indications for induction on the ward and private services.

At various times, patients with all types of toxemia, both hypertensive and pre-eclamptic, have been subjected to induction of labor with oxytocin. During these 2 years we have records of only one eclamptic patient in whom labor was induced, but we would certainly not hesitate to induce labor in such a patient as soon as she was under

Table I. Success of induction

	Ward patients (152)	Private patients (389)
Successful (first attempt)	98.7% (150)	95.8% (373)
Successful (second attempt)	1.3% ( 2)	2.8% ( 11)
Failure	0% ( 0)	1.5% ( 5)

Table II. Results of induction

	Ward patients (152)	Private patients (389)
First stage less than 10 hours	92.1% (140)	92.0% (358)
Spontaneous delivery	55.9% ( 85)	52.4% (204)
Premature infants	11.1% ( 17)	3.5% ( 14)
Oversized infants	5.2% ( 8)	10.5% ( 41)
Fetal distress	7.2% ( 11)	5.9% ( 23)
Neonatal mortality (corrected)	0% ( 0)	2.8% ( 11)

Table III. Indications for induction

	Ward patients (152)*	Private patients (389)
Toxemia	23.0% (35)	17.4% ( 69)
Diabetes	5.9% ( 9)	6.6% ( 26)
Other medical indications	30.2% (46)	6.9% ( 27)
Obstetrical	36.1% (55)	46.2% (180)
Elective	19.8% (30)	22.3% ( 87)

\*Some patients had more than one diagnosis.

satisfactory control unless more rapid delivery by cesarean section seemed advisable.

Generally speaking, if there are no obstetrical reasons to the contrary, attempts are made to induce labor in patients with diabetes at about the thirty-sixth or thirty-seventh week. If necessary, 4 or 5 attempts at induction with oxytocin are made on successive days in these patients before resort is made to cesarean section.

There is a rather general group of cases classified under "other medical," consisting of patients with both active and inactive pulmonary tuberculosis and active and inactive rheumatic heart disease, some of whom were actually in failure, and two cases of "unclassified pulmonary disease" the nature

of which was not clear from the chart.

The "obstetrical indications" were also somewhat general and consisted of the following: rising anti-Rh titer, prolonged rupture of membranes with a viable fetus, "cervical bleeding," marginal placenta previa, "secondary uterine dysfunction," and postmaturity. It is interesting that in these 2 years we have records of only 6 cases of induction with oxytocin being carried out in patients with previously diagnosed fetal intrauterine death. The staff may have become cautious in this situation because of the possibility of hypo- and afibrinogenemia in a severe and rapid labor that might possibly be produced by induction of labor with oxytocin.

Of the 541 inductions during the 2 years, 117 or 21.6 per cent were elective. These at first were more frequent on the private service but during 1958 and at the present time the percentage of elective inductions on the two services were about the same.

The reasons for "elective induction" are many and varied and occasionally somewhat bizarre. Obviously, no elective induction for the convenience of either the patient or the obstetrician should be carried out unless there is no question in the experienced obstetrician's mind that the cervix is negotiable and that labor is inducible. We heartily agree with the "rules of conduct" described by Bishop,<sup>12</sup> in which he states that it is most important for the patient to be fully aware of the reasons for the induction and that this procedure should certainly not be carried out if the patient or her husband has any doubts whatever concerning its advisability.

It is unnecessary to describe what should be considered a "negotiable" cervix, but this type of cervix plus an engaged fetal head should certainly be prerequisites of elective induction.

There is a difference of opinion as to whether or not amniotomy should be performed before induction with oxytocin is begun. One point of view is that, should an oxytocin infusion be started and the induction prove to be a failure, no harm is done and the patient may be allowed to go into

labor spontaneously later or another induction attempted at a later date. On the other hand, if amniotomy is performed, one is committed to delivery of the patient by one means or another within the next day or two. It is the authors' opinion that *if* the obstetrician is experienced enough to identify without question the negotiability of the cervix and the position of the fetal presenting part, amniotomy is of great assistance in achieving a successful induction. In fact, under these circumstances the use of an oxytocin infusion is frequently unnecessary. If there is any question whatever in the obstetrician's mind concerning the possibility of failure to initiate the onset of labor by amniotomy plus oxytocin infusion, then the latter should be begun first and, in the event of failure, repeated later if necessary.

We also fully agree with Bishop<sup>12</sup> that the patients appropriate for elective induction constitute a highly selected group of not much over 20 to 25 per cent of all pregnancies and that when the number of elective inductions exceed this, difficulties are likely to occur.

### Summary

Under these circumstances then, during the years of 1957 and 1958 there were 541 inductions of labor with oxytocin. There were no maternal deaths and 2.04 per cent (corrected) fetal mortality. There were no ruptured uteri; the type of delivery was approximately the same as with the uninduced labor, and the obstetrical complications such as cervical laceration, amniotic fluid embolus, tetanic contractions, and precipitate labor were not increased.

### Conclusions

As is the case with practically every other valuable drug, oxytocin is potentially extremely dangerous for both the mother and the fetus when used before delivery. If appropriate precautions are taken, however, and safeguards strictly adhered to, oxytocin for induction of labor and correction of secondary uterine inertia can be of immense value in the practice of obstetrics.

REFERENCES

1. Watson, B. P.: *Canad. M. A. J.* 3: 739, 1913.
2. Blair-Bell, W.: *Brit. M. J.* 2: 1609, 1909.
3. Hofbauer, J., and Hoerner, J. K.: *AM. J. OBST. & GYNEC.* 14: 137, 1927.
4. Watson, B. P.: *Tr. Am. Gynec. Soc.* 45: 30, 1920.
5. Reid, D. E.: *AM. J. OBST. & GYNEC.* 52: 719, 1946.
6. Eastman, N. J.: *AM. J. OBST. & GYNEC.* 53: 432, 1947.
7. Quigley, J. K.: *AM. J. OBST. & GYNEC.* 53: 439, 1947.
8. Theobald, G. W., Graham, A., Campbell, J., Gange, P. W., and Driscoll, W. J.: *Brit. M. J.* 2: 123, 1948.
9. Theobald, G. W., Kelsey, H. A., and Muirhead, J. M.: *J. Obst. & Gynec. Brit. Emp.* 68: 641, 1956.
10. Pierce, J. G., Gordon, S., and DuVigneaud: *J. Biol. & Chem.* 199: 29, 1952.
11. Hess, O. W., and Hon, E. H.: *In press.*
12. Bishop, E. H.: *J. A. M. A.* 166: 1953, 1958.



# Pregnancy in the woman over forty

ALBERT L. HIGDON, M.D.

*Teaneck, New Jersey*

PREGNANCY has been likened to athletic performance in that the capacity to undertake it efficiently falls off very rapidly with age,<sup>1</sup> and a woman is obstetrically old before she is chronologically old. Numerous reports have appeared in the literature citing the dangers of pregnancy in the elderly woman.<sup>2-6</sup> Although there is not universal agreement as to what these risks are, some more frequently mentioned are an increase in vascular disease and its counterpart, toxemia, an increase in operative deliveries, malpresentations, fibroids, placenta previa, abruptio placentae, prolonged labor, and blood loss. The fetus is subjected to the dangers of these complications and hence there is an increase in stillbirths, premature infants, neonatal deaths, and abnormalities.

Most of these studies concern themselves with the pregnant woman over 35 years of age and largely with the primigravida. This report limits itself more in that it deals only with pregnancy in women over 40 years of age. These women were all delivered in a private suburban hospital, and most of them enjoyed a higher than average socioeconomic status. A substantial number are from my own practice, and many others were seen by me in consultation.

## Material

Between Jan. 1, 1950, and Dec. 31, 1958, at Holy Name Hospital in Teaneck, New Jersey, 22,022 babies weighing over 1,000 grams were born (Table I). There were 204

sets of twins born to the 21,818 mothers. Of this number 522 (2.44 per cent) were women over 40 years of age, and they gave birth to 7 sets of twins. Although 522 is not a large enough number to be statistically significant, it does represent the 9 year product of one community hospital and one should be able to detect certain trends.

## Delivery distribution

Thirty men engaged in general practice delivered 235 (45 per cent) of the patients, and 10 specialists in obstetrics and gynecology delivered the others (Table II). A friendly, cooperative relationship prevails between the two groups. Consultations are sought frequently and are given without hesitation. The consultations, as well as cesarean sections and most difficult deliveries, are done by the obstetricians.

## Age and parity

Table III and Table IV reveal the age and parity distribution; 305 (58 per cent) of the women were 40 to 41 years of age; 32 (6 per cent) of the group were primigravidae, and although this is a small number, some interesting facts about this group will be presented later.

## Length of labor

The forces of labor functioned very well in this group (Table V); 371 (76 per cent) of the patients who delivered vaginally had labors of 10 hours or less. Only 21 (3.9 per cent) had labors over 20 hours in duration. This compares favorably with most statistics for women in younger age groups. Two labors were induced for convenience and 2 for toxemia.

*From the Department of Obstetrics,  
Holy Name Hospital.*

*Presented at the Fifteenth Annual  
Meeting of the Society of Obstetricians  
and Gynaecologists of Canada, Mont  
Tremblant, Quebec, Sept. 11-13, 1959.*

**Table I.** Deliveries of women over 40 years of age at Holy Name Hospital (Jan. 1, 1950, to Dec. 31, 1958)

Mothers delivered	21,818
Average deliveries per year	2,424
Babies born	22,022
Mothers over 40	522 (2.44%)

**Table II.** Classification of deliveries according to medical attendant

General practitioner	235
Specialist	139
Author	148
Total	522

**Table III.** Age distribution of the group over 40 years old

Age (years)	No. of patients
40	187
41	118
42	84
43	57
44	44
45	20
46	10
47	2
Total	522

#### Weights at birth

Contrary to some reports, the incidence of premature infants did not appear to be increased (Table VI); 27 (5 per cent) of the newborn infants weighed less than 2,500 grams. However, 78 (13.7 per cent) weighed over 4,000 grams, which is a higher percentage than is usually reported for infants born to younger women.

#### Method of delivery

The incidence of operative deliveries was increased (Table VII); 211 (40 per cent) were spontaneous. Although 198 (37 per cent) were delivered by low forceps, a large number of these were low prophylactic forceps. There were 49 (9.2 per cent) midforceps deliveries, which seems quite high. Most of these were because of occiput transverse

or posterior positions. Forty-three (8.2 per cent) of the patients were delivered by low flap cesarean section.

#### Fetal position

Table VIII classifies fetal position, and in this age group it would appear that there is a slight increase in breech and brow presentations and in occipitotransverse and occipitoposterior babies which failed to rotate.<sup>7</sup>

#### Cesarean sections

There were 43 low flap cesarean sections for an over-all rate of 8.2 per cent (Table IX). This represents a marked increase over the general hospital rate (3.8 per cent) for the same period of time. However, the increased prevalence of repeat sections in this age group as compared to a younger age group would distort these figures to some extent. The principal indications for cesarean section (Table X) are repeat section,

**Table IV.** Parity distribution of the group over 40 years old

Parity	No. of patients
0	32 (6%)
1	80
2	121
3	113
4	73
5	51
6	23
7	14
8	9
9	2
10	3
11	1
Total	522

**Table V.** Length of labor

Length of labor (hours)	No. of patients
0-5	197
5-10	174
10-15	65
15-20	28
20-25	10 (1.9%)
Over 25	11 (2.0%)

Table VI. Weight of infant

Weight (grams)	No. of infants
1,000-1,499	2 ( .37%)
1,500-1,999	5 ( .94%)
2,000-2,499	20 (3.7%)
2,500-2,999	74
3,000-3,499	193
3,500-3,999	157
4,000-4,499	58 (10%)
4,500 and over	20 (3.7%)

Table VII. Method of delivery

Method	No. of patients
Spontaneous	211 (40%)
Low forceps	198 (37%)
Mid forceps	49 (9.2%)
Breech extraction	24
Version and extraction	3
Cesarean section	43 (8.2%)
Total	528

Table VIII. Presentation and position of the fetus

Left occipitoanterior	268	
Right occipitoanterior	181	
Breech	29 (5.4%)	
Brow	2 (0.37%)	
Transverse lie	1	
Left occipitotransverse	4	9.0%
Right occipitotransverse	9	
Left occipitoposterior	14	
Right occipitoposterior	21	

dystocia, and hemorrhage. We have followed the dictum of "once a section, always a section." All 5 patients with cephalopelvic disproportion had an adequate trial of labor. The elderly primiparas with breech presentation had no trial of labor because of the position and high social value of the baby. All infants delivered by cesarean section lived.

#### Maternal complications

The principal maternal complications were toxemia and hemorrhage (Table XI). In this series there were 20 (3.8 per cent) cases of toxemia, which is below the expected average. The explanation of this low incidence may lie in the fact that all of these

were private patients whose general prenatal care, health, and nutritional status may have been better, and their concern for detecting and reporting any danger signals may have been more acute than the general obstetrical population. Placenta previa and abruptio placentae (2.5 per cent) occurred less often than in most series. Postpartum bleeding was encountered in 22 (4.2 per cent) patients. Although this figure is not high, a more careful observation of the fourth stage of labor would probably lower the incidence of atony of the uterus. Seven additional patients had postpartum transfusions because of anemia. This may have been present before delivery, or the blood loss may have been underestimated. One patient had a postpartum hysterectomy a few minutes after delivery because of placenta accreta. Four patients had heart disease, and 2 had acute congestive failure in the last trimester but recovered and did well thereafter. Fibroids, which in one patient necessitated cesarean section, were noted 8 times. The maternal morbidity was infinitesimal and there were no maternal deaths.

Table IX. Frequency of cesarean sections as compared to general hospital rate

Patients over 40	43 (8.2%)
First sections	23 (4.4%)
Repeat sections	20 (3.8%)
Hospital total all ages	837 (3.8%)

Table X. Indications for cesarean section

Previous section	20 (46%)
Dystocia	9 (21%)
Cephalopelvic disproportion (all with trial labors)	5
Breech (elderly primipara)	2
Transverse lie	1
Fibroid obstructing pelvis	1
Hemorrhage	9 (21%)
Placenta previa	5
Abruptio placentae	4
Toxemia	1
Advanced malignancy	1
Previous rupture of uterus	1
Previous extensive perineal repair	1
Primary inertia	1
Total	43



Table XI. Maternal complications

<b>Toxemia</b>	
Pre-eclampsia	7
Hypertension	9
Hypertension and toxemia	4
	<hr/> 20 (3.8%)
<b>Hemorrhage</b>	
<i>Antepartum</i>	
Placenta previa	6
Abruptio placentae	7
	<hr/> 13 (2.5%)
<i>Postpartum</i>	
Atony	10
Cervical laceration	3
Perineal hematoma	1
Placenta accreta (hysterectomy)	1
Anemia with transfusion	7
	<hr/> 22 (4.2%)
<b>Others</b>	
Heart disease	4
Thrombophlebitis	9
Pyelitis	5
Hydramnios	2
Wound disruption	1
Carcinomatosis	1
Fibroid uterus	8
Bladder atony	3
Prolapsed cord	1
Postpartum psychosis	2
Postpartum pneumonia	1

#### Fetal complications

In this group, the chances of fetal survival were not reduced as often reported. The fetal loss numbered 12 (2.2 per cent) (Table XII). Fourteen infants (2.6 per cent) had anomalies and 6 were too severe to be compatible with life. There were 11 (2.0 per cent) Mongoloids, which is in agreement with other observations.

#### Primiparas

The 32 primiparas in this series, though too small a number to be significant, had a very poor record (Table XIII). They had an increase in prolonged labor, operative deliveries, abnormal positions, and maternal complications.

#### Psychological aspects

Considerable reference has been made to the psychic impact of pregnancy in these

elderly women. It is said that they are not prepared for pregnancy at this age and need more support, guidance, and counsel. Among my patients (148), this observation was not made. These women had had 40 or more years to mature and as a group behaved maturely. They appeared to be as happy being pregnant as any other women, and were generally easier to manage psychologically than their much younger pregnant sisters.

#### General comment

This is a study of 522 women over the age of 40 delivered in a private suburban hospital.

It was found that the duration of labor is not increased. Midforceps are used more often, and the cesarean section rate is higher than the general obstetrical population.

The principal maternal complications are toxemia and hemorrhage, but neither is as high as is usually reported for this age group. Toxemia especially is seen less often than expected, and it is suggested that the general health and nutritional status of this above average income class group could possibly account for this. It is also believed that a closer observation of the fourth stage of

Table XII. Complications among 522 infants

<b>A. Complications resulting in fetal loss</b>	
Congenital anomalies	6
Intracranial hemorrhage	2
Pneumonia and empyema	1
Rh disease	1
Abruptio placenta	1
Maceration (cause?)	1
	<hr/> 12 (2.2%)
<b>B. Complications in surviving infants</b>	
Mongoloids	11 (2.0%)
Cleft palate	3
Foot deformities	3
Hemangioma	1
Pyloric stenosis	1
Facial paralysis	1
Cord hemorrhage	1
Rh disease with replacement transfusion	3
	<hr/> 24

**Table XIII.** Summary of 32 primiparas over 40

Labor under 20 hours	21
Labor over 20 hours	7
Cesarean section	7 (21%)
Trial labor	3
No labor	4
Spontaneous deliveries	0
Low forceps	18
Mid forceps	7
Position	
Vertex anterior	23
Vertex transverse or posterior	5
Breech	3
Transverse lie	1
Complications	
Maternal	
Pre-eclampsia	3
Placenta previa	1
Laceration of cervix	1
Fibroid obstructing pelvis	1
Fetal	
Pyloric stenosis	1
Death (intracranial hemorrhage)	1

labor can reduce even further the frequency of hemorrhage. Placenta previa and abruptio placentae do not occur more often. Heart disease is more common than in the younger age group.

Premature infants (less than 2,500 grams) are no more frequent, but infants weighing over 4,000 grams are more prevalent. Fetal mortality is not above that of the general population, but Mongoloids do occur more often.

The dangers of pregnancy in the elderly woman are perhaps exaggerated. No doubt the aging process does increase certain systemic ailments, but if one is aware of this fact and gives of his very best to his patient, complications in pregnancy can be lowered. As a group, women over 40 should not be denied the right to pregnancy, for under good obstetrical care they can approach pregnancy optimistically.

## REFERENCES

1. Lancet 1: 507, 1959.
2. Kaltreider, D. Frank: Obst. & Gynec. 13: 190, 1959.
3. Weaver, R. T., and Johnson, Fred L.: Canad. M. A. J. 80: 163, 1959.
4. Calkins, L. A.: J. A. M. A. 141: 635, 1949.
5. Weisl, B. A.: AM. J. OBST. & GYNEC. 66: 1235, 1953.
6. Waters, E. G., and Wager, Henry P.: AM. J. OBST. & GYNEC. 59: 296, 1950.
7. Titus, Paul: Revised by Willson, J. Robt.: Management of Obstetrical Difficulties, ed. 5, St. Louis, 1955, The C. V. Mosby Company, p. 423.

773 Teaneck Road  
Teaneck, New Jersey

## GYNECOLOGY

### Details of pelvic exenteration evolved during an experience with 75 cases

ROBERT L. SCHMITZ, M.D.  
HERBERT E. SCHMITZ, M.D.  
CHARLES J. SMITH, M.D.  
JOHN J. MOLITOR, M.D.\*

*Chicago, Illinois*

PELVIC exenteration involves excision of the genitals and pelvic lymphatic tissues along with the bladder (anterior exenteration) or the rectum (posterior exenteration) or both (total exenteration). Whether the vulva, urethra, and anus are included in whole or in part varies with the surgeon's technique.

These operations are still not widely accepted; they are considered by many to be too radical, to have too high a mortality rate, and to have too low a survival rate. Yet, in many instances of cancer of pelvic viscera when more conservative treatment is inadequate or has failed, the only alternative to exenteration is a progressively downhill course fraught with pain, toxemia, or hemorrhage and ending in death.

*From Stritch School of Medicine at Loyola University and the Mercy and Lewis Memorial Hospitals.*

*Supported by the Henry Schmitz Medical Foundation.*

*Presented at the State University of New York, March 10, 1959.*

*\*Fellow, American Cancer Society.*

There is a continuing need for those who do these procedures to report any modifications of or adjuncts to the operation which may improve the results.

#### **Chronology of our series**

In March, 1947 we performed our first exenteration. It was of the posterior type and was for a carcinoma of the cervix which was recurrent after irradiation therapy and which extended into the rectum. The patient had a stormy postoperative course complicated by ureteroperineal fistulas and pyelonephritis and died on the fifty-third postoperative day.

By December, 1947, we found our courage again and performed our second exenteration, this time of the anterior variety, for a recurrent carcinoma of the cervix invading the bladder. The ureters were implanted into the sigmoid. The patient had a smooth convalescence and left the hospital 20 days later. She is still alive and well with normal intravenous pyelograms and normal blood chemistry determinations.

In May, 1948, we performed our third



exenteration, a posterior type for recurrent carcinoma of the cervix invading the rectum. This patient had a smooth course and left the hospital on the fifteenth postoperative day. She is also still living and well.

With these last 2 cases to encourage us we continued slowly during the next 2 years and performed 6 more (Table I): one posterior, two anterior, and three total operations, but only the patient on whom the posterior exenteration was performed lived. We had only 3 living patients out of 9 operated upon during a 4 year period, and we were not very well impressed.

During 1951 we sat back and watched our 3 survivors. They were doing well and others<sup>1, 4, 7</sup> were reporting encouraging results with the operation, so by 1952 we were willing to try again. By the end of 1958 we had performed 75 exenterations (Table I). Now we are convinced that the operation has a place in the treatment of cancer of the pelvic organs, especially of the cervix.

#### Indications for exenteration

In the majority of instances, the indication for exenteration is recurrent carcinoma of the cervix (Table II). There are occasional instances in which recurrent cancer of other parts of the genital tract or the lower urinary tract or the rectum will lend itself anatomically to exenteration, and there are occasional instances in which a primary untreated malignancy of these organs may best be attacked initially by such an operation. Finally, severe radionecrosis accompanied by vesicovaginal and/or rectovaginal fistulas may necessitate exenteration because recurrent cancer cannot be ruled out and because the fistulas are incompatible with continued well-being and cannot be corrected by any lesser procedure.

Recurrent cancer actually is persistent cancer which has failed to respond to the initial treatment, and in cancer initially treated by adequate irradiation it implies radioresistance of the cancer. It is therefore logical that the secondary attack in such a situation should be surgical and as radical as the circumstances permit.

Table I. Exenterations: chronology

Year	Type of exenteration			All cases
	Anterior	Posterior	Total	
1947	1	1	0	2
1948	1	1	0	2
1949	1	0	1	2
1950	0	1	2	3
1951	0	0	0	0
1952	2	2	7	11
1953	2	2	3	7
1954	4	1	0	5
1955	2	6	1	9
1956	6	2	1	9
1957	3	1	2	6
1958	0	1	18	19
Total	22	18	35	75

Our initial treatment of carcinoma of the cervix is still irradiation therapy in most cases. As soon as recurrent (persistent) disease is manifest, operation is advised. The choice of radical hysterectomy or exenteration is tentatively made on the basis of the preoperative work-up but is finally determined at the time of operation.

Corpus carcinoma is treated initially by irradiation therapy followed in 6 to 12 weeks by hysterectomy. An occasional case of localized recurrence in the cul-de-sac or vaginal vault will be suitable for exenteration.

The widespread peritoneal seeding which accompanies most recurrent ovarian cancers makes exenteration an illogical procedure for this situation. But in instances of well-localized recurrences the operation may be applied.

Rectal cancer invading the vagina or upper genitals may be suitable for posterior exenteration, while cancer of the bladder which invades these structures may be suitable for anterior exenteration.

#### Selection of patients

Two extremes must be guarded against in selecting candidates for the operation. Cases that can be adequately treated by more conservative measures, e.g., the inadequately irradiated radiosensitive cancer that will still respond to proper irradiation or the

fairly localized recurrent cancer that can be treated by the radical excision of a single organ alone, should not be chosen. On the other hand, we must be discriminating enough to try not to subject to operation cases that are too far advanced, lest our results be so poor that the operation will fall into disrepute.

Obviously, no patient with proved metastases beyond the extent of the pelvic resection is a candidate; we would include even solitary metastases in the lung or liver as a contraindication to an operation of this magnitude.

Edema in one or both legs is a contraindication if the history and pelvic examination suggest it is from compression of the vessels by tumor rather than from incidental thrombophlebitis.

Extreme fixation of the pelvic tissues laterally usually means inoperability, but this situation is worthy of surgical exploration before the patient is denied exenteration since several such cases have been easily operable and several have demonstrated only inflammation and radionecrosis on pathological examination.

The patient's general health should be good; there should be no serious chronic

disease threatening life. As long as the patient has a reasonable life expectancy (5 to 10 years), age is no contraindication. Many of our patients have been in their 60's—one 69—but so far we have had none older.

If preliminary work-up reveals no contraindication, the patient is subjected to surgery. At operation, the final decision as to operability is made, i.e., there are no hepatic or peritoneal or nodal metastases beyond the pelvis, and there is no local pelvic invasion that would preclude the removal of all tumor tissue that can be grossly identified. In cancer of the cervix, if the tumor is well confined to the cervix and vagina with or without palpable pelvic nodes, only a radical hysterectomy is performed, but, if there is any extension anteriorly or posteriorly, an exenteration is done.

#### Preoperative preparation

**Medical evaluation.** This includes an electrocardiogram, chest x-ray examination, complete blood count and hematocrit determination, measurement of the blood sodium, potassium, chloride, carbon dioxide combining power, urea and sugar, proctoscopy, cystoscopy, and intravenous pyelography. Any corrective therapy (e.g., digitalization, regulation of diabetes, blood transfusion) is carried out.

**Bowel preparation.** The patient is placed on a low-residue diet. Two grams of Sulfasuxidine is administered every 6 hours for 5 to 7 days before the operation. During the 48 hours immediately preceding operation 500 mg. of neomycin is given every 6 hours. A dose should be given the morning of the operation. Purging is not done, although a single dose of phosphosoda may be given 2 to 3 days preoperatively if the patient's bowels have been sluggish. A cleansing enema is given on the evening before the operation.

**Intestinal decompression.** This is important during the postoperative period and for this purpose a long gastrointestinal tube (Miller-Abbott or Cantor) is inserted about 24 hours preoperatively so that it will have

Table II. Exenterations: site of disease and indications for operation

Site of disease	Indication for operation	Type and No. of exenterations			Total No. of cases
		Anterior	Posterior	Total	
Urethra and bladder	Recurrence	4	—	—	4
	Radionecrosis	1	—	—	1
Vulva	Recurrence	—	—	1	1
Vagina	Recurrence	1	—	1	2
Cervix	Recurrence	14	10	26	50
	Radionecrosis	1	3	2	6
Corpus	Recurrence	1	1	2	4
Ovary	Recurrence	—	2	1	3
	Primary lesion	—	—	1	1
Rectum	Recurrence	—	1	1	2
	Primary lesion	—	1	—	1
Total		22	18	35	75

time to enter the small bowel. No suction is applied to it until after the operation. If a gastrostomy tube is placed at the conclusion of the operation it obviates the need for the long tube.

**Blood replacement.** Blood replacement is carried out preoperatively if indicated, but, regardless, each patient is crossmatched for 2,500 c.c. of whole blood to be available during the operation. A sample of the patient's blood is kept in the blood bank for further crossmatching, should the need arise.

**Cannulization of an ankle vein.** Cannulization with a 15 gauge polyethylene tube is carried out immediately preoperatively. This tube is left in for 3 or 4 days postoperatively for the parenteral administration of electrolytes and medications.

#### Extent of the operation

The details of the technique of exenteration have been well described by Meigs.<sup>6</sup> As we have stated, the vast majority of exenterations are performed for carcinoma of the cervix. Until 1958 we used anterior, posterior, and total exenterations in the cervix lesions about equally, depending on what the circumstances seemed to be at operation. However, the vesicovaginal and rectovaginal septa are thin structures, and dissection through them does not give good clearance from the cancer; recurrences locally after a subtotal exenteration are common. In addition, when there has been previous irradiation, the endarteritis in these septa leads to troublesome sloughs of the bladder and rectum if dissection is carried through them. For these reasons we have performed almost all total exenterations for cervix carcinoma since 1957.

For the various other indications, the type of exenteration must be individualized, with the above points kept in mind. As stated earlier, cancer recurrent in the bladder invading the genitals is usually suitable for anterior exenteration, while cancer in the rectum invading the genitals is apt to fit posterior exenteration.

The question of whether or not the per-

ineum should be excised is unsettled. Obviously, if carcinoma extends well down toward it, it would be better to include it in the dissection. This point cannot always be determined on preoperative examination. Several authors who tried routine excision of the perineum for a while have abandoned it as too shocking and of too little curative value.<sup>8, 11</sup> It is true that the levator ani muscles can be excised relatively completely from above and that, with traction during the dissection, portions of the vulva and the anus may even be obtained. However, if two surgical teams work synchronously through abdominal and perineal fields, all of the perineum is easily mobilized by the lower team while the upper team is engaged in the dissection of the lymph nodes. There are other advantages to this technique that will be discussed later.

The value of extensive lymph node dissection might well be questioned. It is usually executed meticulously and completely, and yet it can hardly be done in the en bloc manner so desirable in cancer operations; it can be very time consuming (1 to 2 hours); it may be accompanied by brisk hemorrhage from the cutting or tearing of one of the major pelvic arteries or veins; it may lead to later sloughing of one of these major vessels; it may lead to pelvic thrombophlebitis; it may be followed by obturator nerve or sacral plexus neuritis or palsy. All this risk, and yet it has been shown that if the lymph nodes are involved by tumor there are practically no 5 year survivors.<sup>2, 5, 8, 12</sup> The potential gain is hardly worth the risk. We must at least appraise this step further; to date we have not abandoned it, but it might well be that a modified, less extensive lymph node dissection, taking only that tissue lying medial to the vessels and available without mobilizing or displacing them, would be a more rational procedure.

#### Operating time

These operations take a long time at best (Table III). There are so many different factors involved that it is difficult to make



Table III. Exenterations: operating time

Type of exenteration	Shortest time		Longest time		Average time	
	Hr.	Min.	Hr.	Min.	Hr.	Min.
Posterior	2	30	6	35	3	44
Anterior	2	38	6	0	4	27
Total	2	49	7	15	4	55
All types					4	30

comparisons even within the same anatomical type of exenteration. Hemorrhage may waste as much as an hour while control is attained; in two instances external iliac artery reanastomosis was necessary, and in one instance extensive repair of an external iliac vein was carried out.

The lymph node dissection may take as long as two hours, as has been said previously.

The need for urinary diversion adds time, and some of the more complex methods require up to 2 hours to complete.

Various adjunctive maneuvers also add time, such as gastrostomy or the covering of the pelvic funnel with a lid.

On the other hand, it will be seen that when all goes well even a total exenteration may take only 3 to 4 hours.

#### Blood requirements during operation

All of our patients undergoing exenteration require whole blood during the operations; none less than 1,000 c.c., and an occasional patient who hemorrhaged required as much as 5,000 to 10,500 c.c. The

earliest cases required so much blood that we felt something should be done about it. We tried hypotensive technique and the saving in blood was so worth while (Table IV) that this technique is now routine with us. In 26 cases in which the hypotensive technique was used, less than 2,000 c.c. of whole blood was required while in only 7 cases without use of this technique were such amounts sufficient. It is also true that fewer patients had shock during the operation when the hypotensive technique was used (8 out of 45) than when it was not (10 out of 30). The figures of the average amounts of blood used are impressive even though the series are small and the heavy bleeders weight them in the increased direction.

For hypotension we use Arfonad (a thio-phanium compound). A 0.1 per cent solution is given by intravenous drip starting before the incision is made. The rate of flow is regulated to keep the blood pressure at that level at which excessive bleeding is controlled—this is usually between 80 and 100 mm. Hg for the systolic pressure. The reduction in pressure is maintained throughout the part of the operation during which extensive dissection is being carried out (about 1 to 3 hours), then the drug is stopped and the pressure is allowed to return to normal during the reconstructive phase of the operation. In 45 operations performed with hypotensive technique we have not been aware of any problems from it.

Table IV. Exenterations: blood given during operation

Type of exenteration	Hypotensive technique (No. of cases)	No. given whole blood				Average amount (c.c.)
		1,000-2,000 c.c.	2,500-3,500 c.c.	4,000-7,000 c.c.	7,500-10,500 c.c.	
Posterior	No (9)	4	5	0	0	2,222
	Yes (9)	7	2	0	0	1,611
Anterior	No (7)	2	4	1	0	2,929
	Yes (15)	9	4	1	1	2,200
Total	No (14)	1	10	2	1	3,643
	Yes (21)	10	8	1	2	2,681
All cases	No (30)	7	19	3	1	3,050
	Yes (45)	26	14	2	3	2,284

**Table V.** Two-team exenterations: chronology

Year	Type of exenteration			All cases
	Anterior	Posterior	Total	
1952	1	0	1	2
1953	0	1	0	1
1954	0	0	0	0
1955	2	2	0	4
1956	1	2	0	3
1957	3	0	2	5
1958	0	1	18	19
Total	7	6	21	34

**Table VI.** Two-team exenterations: indications

Site of disease	Type of exenteration			All cases
	Anterior	Posterior	Total	
Bladder	1	0	0	1
Vulva	0	0	1	1
Vagina	0	0	1	1
Cervix	6	5	16	27
Ovary	0	0	2	2
Rectum	0	1	1	2
Total	7	6	21	34

We have from time to time considered the use of hypothermia as a further adjunct, but as yet we have not attempted it.

#### **Synchronous abdominoperineal technique**

We first used synchronous abdominoperineal resection for lesions of the rectum.<sup>9</sup> Two surgical teams work simultaneously, one through the abdomen and one through the perineum. A comparison of this technique with the one-team method revealed that we were saving time, that the operative course was smoother, that no extra blood was required (that is, there was no increased trauma), that the postoperative complications were fewer, and that the mortality rate was lower.

Beginning in 1952, we applied this technique to pelvic exenterations; the details have been presented earlier.<sup>10</sup> The patient is placed in the lithotomy-Trendelenburg position. Once the upper team has nearly completed the node dissection and has tied

off both hypogastric arteries, the lower team mobilizes the entire perineum. The two teams work in unison mobilizing the bladder and rectum and then in transecting the lateral lymphatic webs.

Finally, while one team closes the perineum, the other team accomplishes any reconstruction work, including urinary diversion, and then closes the abdomen.

Since 1952 we have performed 34 of 66 exenterations by this technique (Table V); 18 of the two-team total exenterations were carried out in 1958 alone, pointing to our recent enthusiasm for this approach; in 15 of these 18 cases the indication was carcinoma of the cervix, emphasizing a point we made earlier: we feel that subtotal exenterations are usually inadequate for cervical lesions. The two-team approach was also used in anterior and posterior exenterations and for disease primary in the bladder, vulva, vagina, ovary, and rectum (Table VI).

Actually, a comparison of the operations performed by the one-team and two-team techniques so far shows no significant differences, but the series are so small and the variables so many that this is not surprising. Certainly it is our impression that this approach has advantages technically and we feel objective evidence will be forthcoming shortly.

**Table VII.** Exenterations: methods of urinary diversion

Type of diversion	Anterior ex- enter- ation	Total ex- enter- ation	Total
Skin ureterostomy	2	3	5
Ureterosigmoidostomy	17	—	17
Ureterosigmoidocolostomy (wet colostomy)	—	12	12
Ureterosigmoidocolostomy with proximal colostomy (Parson's)	—	3	3
Ureteroileosigmoidostomy (Turnbull)	1	—	1
Ileal conduit (Bricker)	2	17	19
Sigmoid conduit	—	4	4

### Pelvic lids

Usually after exenteration the empty pelvic funnel is left wide open since there is no peritoneum available to cover it. Some surgeons fill the funnel with a gauze packing not only for hemostasis but to keep the small intestine up and out of it until the bowel is fixed at a higher level by adhesions. Others deliberately place the small intestine into the empty pelvis to obliterate this space.

However, small bowel obstruction in the deep pelvic funnel, small bowel-perineal fistula, and perineal herniation are not infrequent early or late complications of exenteration in our experience as well as in that of others. For these reasons we think it may be desirable to cover the empty pelvis with a lid.<sup>10</sup> This has been attempted in 15 cases to date with various materials which had already been used in the laboratory as well as clinically for replacing defects in the diaphragm and in the abdominal wall.

In 4 instances Ivalon was used, in 10 instances tantalum or steel mesh, and in one instance Marlex mesh. After the exenteration is completed and before urinary diversion is begun, a sheet of the material selected is sewn to the inner pubic area, along the lateral abdominal walls, to the iliopsoas muscles and to the presacral tissues near the promontory. When a pliable material such as Ivalon or Marlex is used, it can be sutured in part to the cut edges of the peritoneum.

In a few cases the pelvis below the lid has been packed with gauze for hemostasis, but in most instances the perineum was closed tightly about a bundle of Penrose drains.

Following the placing of a lid, the empty pelvis below has to obliterate by fibroplasia. This can be a slow process, and in several instances there has been some serous drainage through the perineum for as long as 6 months. In two of the cases in which Ivalon was used a snug Ivalon plug was packed into the pelvis below the lid in an effort to obliterate this space more rapidly. There proved to be so much increased drainage,

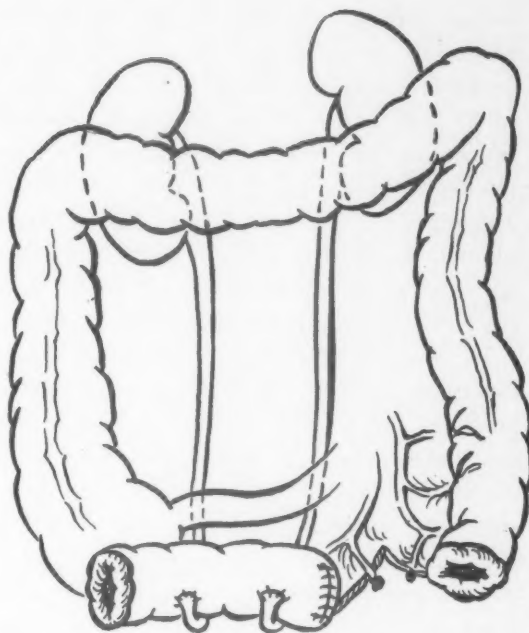


Fig. 1. Sigmoidal conduit. After total exenteration, if enough sigmoid remains, a short segment of it may be isolated with attached mesentery and blood supply to serve as an urinary conduit. The isolation of a segment of terminal ileum followed by ileoileostomy is not necessary.

however, that these plugs (which had become infected) had to be removed through the perineum. We have seen no ill effects from these lids as yet. Several have been in over one year. In several cases that came to autopsy, the mesh seemed to be covered with a glistening membrane with minimal adhesions of bowel to it.

### Urinary diversion

After anterior or total exenteration it is necessary to transplant the transected ureters. This can be and has been done in many ways; in these 75 cases we employed the methods outlined in Table VII. In addition to the methods listed here we have had experience with the Gilchrist ileocecal bladder in 6 instances of nonexenteration operations.

It is not the purpose of this paper to argue the pros and cons of the various types of procedures. When the preoperative studies show normal intravenous pyelograms and normal blood urea values we will still



do ureterosigmoidostomy in an anterior exenteration because it is so much more acceptable to the patients than the various other possibilities. If urinary tract complications develop after ureterosigmoidostomy (hydronephrosis, hyperchloremic acidosis, or ascending pyelitis), the ureters can be transplanted to an ileal conduit and the patient will regain adequate function of the urinary tract. We have done this in three instances.

In general, however, it is best to collect the urine outside the body as promptly as possible. Since skin ureterostomy has not been satisfactory in our hands and since the wet colostomy carries with it a high incidence of ascending infection, we prefer an enteric conduit of some sort. After use of the Bricker ileal conduit for some time with great satisfaction, it occurred to us that in total exenterations a short stump of sigmoid might be mobilized from the proximal end of the divided bowel before the colostomy was established and that this would make a satisfactory conduit, since it could be kept short and there would be no stasis (Fig. 1). Such a maneuver saves the time and morbidity of the ileoileostomy which is a necessary part of isolating an ileal conduit.

We have done this in 4 cases now with complete satisfaction.

While all the other procedures have had multiple instances of various genitourinary tract complications (50 per cent in wet colostomy, for example) the ileal and sigmoidal conduits stand alone with only two instances of minor pyelitis to blemish their records.

#### Postoperative care

In the postoperative care of these patients, in addition to the usual measures, we emphasize several points:

**Antibiotics.** In general, we do not favor antibiotic prophylaxis in surgery, but exenterated patients are so prone to numerous infections (wound, urine, blood) that we give them erythromycin, 500 mg. intravenously, twice a day for 5 days after the operation.

**Table VIII.** Exenterations: postoperative complications

Site	Complications	No.	Total
Urinary tract	Pyelonephritis	13	22
	Fistula	5	
	Lower nephron nephrosis	4	
Cardio-vascular	Hemorrhage	8	15
	Pulmonary embolism	4	
	Septicemia	3	
Gastrointestinal tract	Fistula	5	13
	Severe ileus	4	
	Obstruction	4	
Liver	Jaundice with hepatitis and failure	10	10
Wound	Dehiscence	6	9
	Infection	3	
Pulmonary	Embolism (above)	4	8
	Atelectasis	2	
	Pneumonia	1	
	Empyema	1	
Sepsis	Septicemia (above)	2	5
	Wound (above)	3	
Miscellaneous	Coronary thrombosis	1	2
	Tetany	1	
Total (omitting duplications as indicated above)			75

**Whole blood.** There is always considerable serosanguineous drainage from the perineal wound during the early postoperative period. This loss is reflected in the blood cell, hemoglobin, and protein values so consistently that we routinely give 500 c.c. of whole blood on the first and on the third postoperative days.

**Intestinal decompression.** These patients have prolonged ileus and often a partial mechanical obstruction as well, if an ileoileostomy has been carried out. As stated above, a long gastrointestinal tube (Miller-Abbott or Cantor) is passed preoperatively and is usually well over into the small intestine at the time of the operation. Suc-

tion is applied to this tube immediately after the operation and is continued until the patient is passing gas freely and has a bowel movement—usually 4 or 5 days.

There are disadvantages to this method of decompression, however. The tube does not always leave the stomach, and it is far less effective there than in the small bowel. There is sometimes gastric dilatation from pylorospasm even when the tube is working well in the bowel below. Some patients will not tolerate the tube for a long enough period. Occasionally there is a recurrence of ileus or partial obstruction after the tube has been removed.

For these reasons, we have recently been establishing a gastrostomy at the conclusion of the exenteration by means of a multi-

fenestrated Levine tube or a Foley catheter. It can be left in several weeks if indicated.

**Management of the ileal stoma.** If the skin about the ileal stoma is allowed to be wet with urine it may break down and make the application of a collecting bag at a later date difficult. This seemingly small complication can be so costly in hospital time to the patient that every precaution should be exercised to prevent it. A catheter, regardless of type, dwelling in the conduit is not the answer. We now apply a temporary bag immediately at the end of the operation and keep it glued on at all times, shifting to the patient's custom-made bag as soon as it is ready.

#### Postoperative course

Exenteration patients are prone to major postoperative complications and in this area lie the main stumbling blocks associated with these operations. About half of the patients will develop some significant problem. The various types and their incidence in our cases are listed in Table VIII. Usually two or more occur in the same patient. It is not surprising that the urinary tract complications should lead the list, but the use of the conduit type of diversion may well lower the number of these. We are hoping that the pelvic lid will decrease the number of gastrointestinal tract complications. As the hypotensive technique reduces the amount of blood replacement necessary, the incidence of jaundice and hepatitis should diminish. It is interesting that our patients had a low level of pulmonary and thromboembolic complications.

#### Mortality and survival

Of the 75 patients, 21 died within 30 days of the operation, an over-all mortality rate of 28 per cent; of the 66 patients seen since 1952, 15 died within 30 days, a mortality rate of 23 per cent; of the last 20, 2 died, a mortality rate of 10 per cent (Table IX).

Of the original 75 patients, 4 more died within 30 to 90 days of the operation and 27 more at later dates, so that 23 are still

Table IX. Exenterations: mortality figures

No. of operations	No. dead within 30 days	Mortality rate (%)
All 75	21	28
66 since 1952	15	23
Last 20	2	10

Table X. Exenterations: survival figures

Survival	Total cases		Cases done 2 or more years ago	
	Dead	Alive	Dead	Alive
30 days post-operatively	21	54	16	35
90 days post-operatively	25	50	19	32
1 year post-operatively	45	30	35	16
To date	52	23 (31%)	42	9 (18%)

Table XI. Exenterations: causes of early deaths

	0-30 days	30-90 days
Uremia	7	3
Hemorrhage	5	
Liver failure	3	
Bowel obstruction	3	
Heart failure	1	
Pulmonary embolism	1	1
Septicemia	1	
Total	21	4

**Table XII.** Exenterations: causes of late deaths

Uremia	4	(No cancer)
Recurrent carcinoma	18	
Unknown cause	3	
Miscellaneous		
Cardiovascular arrest	1	(No cancer)
Cardiac arrest during minor surgery	1	(No cancer)
Total	27	

living at present (Table X). In general, those patients who survive the operation for 2 years without recurrence are apt to live on unless an incidental illness takes their lives. If we take only the 51 operations performed 2 years or more ago, our potential 5 year survival rate is 18 per cent. The various causes of early deaths are listed in Table XI and those of late deaths in Table XII.

In several larger series than ours<sup>3, 8, 11</sup> the records suggest that, as skill in technique and care is gained, the mortality rate will approach 10 per cent and the 5 year survival rate 25 per cent.

### Summary

1. Seventy-five pelvic exenteration operations performed from 1947 to 1958, inclusive, are analyzed.

2. Statistics are presented in regard to operating time, blood requirements during operation, postoperative complications, mortality rate, and survival time.

3. The operations are considered from the standpoint of indications for operation, selection of patients, pre- and postoperative care, extent of the procedure, the synchronous (two-team) abdominoperineal technique, the use of a "pelvic lid," and urinary diversion.

### REFERENCES

1. Bricker, E. M., and Modlin, J.: *Surgery* 30: 76, 1951.
2. Bricker, E. M., Butcher, H. R., and McAfee, A.: *A. M. A. Arch. Surg.* 73: 661, 1956.
3. Bricker, E. M.: *Chicago M. Soc. Bull.* 60: 166, 1957.
4. Brunschwig, A.: *Cancer* 1: 177, 1948.
5. Brunschwig, A., and Daniel, W.: *Surg. Gynec. & Obst.* 103: 337, 1956.
6. Meigs, J. V.: *Surgical Treatment of Cancer of the Cervix*, New York and London, 1954, Grune & Stratton, Inc.
7. Parsons, L., and Bell, J. W.: *Cancer* 3: 205, 1950.
8. Parsons, L., and Taymor, M.: *AM. J. OBST. & GYNEC.* 70: 774, 1955.
9. Schmitz, R. L., Nelson, P. A., Martin, G. B., and Boghossian, H. M.: *A. M. A. Arch. Surg.* 77: 492, 1958.
10. Schmitz, H. E., Schmitz, R. L., Smith, C. J., and Molitor, J. J.: *Surg. Gynec. & Obst.* 108: 351, 1959.
11. Ulfelder, H., and Meigs, J. V.: *New England J. Med.* 246: 243, 1952.
12. Wawro, N. W., and Howe, E. R.: *AM. J. OBST. & GYNEC.* 74: 1275, 1957.



# The cervical cone biopsy-hysterectomy sequence and factors affecting the febrile morbidity

DENIS CAVANAGH, M.D.\*

FELIX RUTLEDGE, M.D.

*Houston, Texas*

THE value of cone biopsy of the cervix prior to hysterectomy for carcinoma in situ is generally accepted. Despite the frequency of this operative sequence and the voluminous literature on intraepithelial carcinoma of the cervix, no reference to febrile morbidity in these cases could be found prior to November, 1958. At that time, Osoba<sup>1</sup> reported a study of 38 patients in whom the time interval between cone biopsy and hysterectomy (cone-hysterectomy interval) varied from 2 days to 8 weeks. He confirmed the widely held impression that these women have a higher febrile morbidity than the average posthysterectomy patient. Furthermore, he found that in 19 of his 20 morbid patients, the time elapsing between conization and hysterectomy had been from 2 to 10 days. He also assessed the effect of such factors as prophylactic antibiotics and associated operative procedures and found no evidence that these influenced the posthysterectomy febrile morbidity. One death occurred in his series.

The present study was undertaken in an effort to answer the following questions:

1. Is the postoperative febrile morbidity significantly higher among patients in whom hysterectomy is performed after cold knife cone biopsy of the uterine cervix?

2. If there is an increased morbidity with the cone-hysterectomy sequence, what are the factors causing this and how may the morbidity be reduced?

3. Is the postoperative period of hospitalization increased in a patient having a cone-hysterectomy sequence as compared with a patient having hysterectomy alone?

## Material and method of study

At The University of Texas M. D. Anderson Hospital and Tumor Institute three groups of patients were investigated:

**A. Cone-hysterectomy group.** The charts of 66 consecutive patients, each of whom had had a cone biopsy of the cervix followed by a total hysterectomy within 120 days, were reviewed. All these procedures were performed by the staff or by residents of The University of Texas M. D. Anderson Hospital and Tumor Institute between Oct. 31, 1951, and Feb. 18, 1959. In each case the following features were noted: age, parity, gravidity, presenting complaint, appearance of the cervix at the first visit, the cone-hysterectomy time interval, the type of hysterectomy and associated procedures, the use of prophylactic antibiotics, the menstrual phase at the time of hysterectomy and the

*From the Department of Gynecology, The University of Texas M.D. Anderson Hospital and Tumor Institute.*

*\*Present address: Department of Obstetrics-Gynecology, University of Miami School of Medicine, Jackson Memorial Hospital, Miami, Florida.*

pathological findings in the hysterectomy specimen. Each in turn was correlated with the postoperative febrile morbidity.

**B. Hysterectomy control group.** A control group of 62 consecutive patients of similar age, ethnic representation, and social class, and having similar operative procedures (exclusive of cervical cone biopsy) carried out by the same surgeons over the same period were likewise analyzed.

The number of posthysterectomy days were noted for each patient in Groups A and B. All specimens were studied by the same group of pathologists, and the final diagnosis on the hysterectomy specimen was noted where available.

**C. Cone biopsy control group.** A series of 69 patients in whom a cone biopsy of the cervix had been performed was studied with a view toward assessing the febrile morbidity due to cold knife conization of the cervix alone.

*Indications for cervical cone biopsy.* The indications for cervical cone biopsy in the 66 patients studied in Group A were: (1) a suspicious or malignant vaginal or cervical smear (Papanicolaou Class III, IV, or V) in the presence of a quadrantal cervical punch biopsy tissue diagnosis short of invasive carcinoma; or (2) a quadrantal cervical punch biopsy tissue diagnosis of carcinoma in situ or atypical epithelial hyperplasia.

*Vaginal antiseptic measures.* No preoperative or postoperative vaginal suppositories were used. At the time of cone biopsy, the preoperative preparation consisted simply of pouring saline into the vagina, for it is considered that rubbing of the cervix damages the cervical epithelium, making interpretation of the biopsy more difficult. Schiller's solution was sprayed from an atomizer to outline the minimum area to be taken in the biopsy. The cone biopsy specimen was taken before dilatation of the cervix and fractional curettage.

At the time of the hysterectomy the preoperative preparation of the vagina was carried out with pHisoHex in both the cone-hysterectomy and hysterectomy groups.

*Standard for assessing morbidity.* Before the investigation was begun it was essential to decide upon a standard of surgical morbidity, for there is no universally accepted definition. In this study we have considered a patient to show morbidity if the oral temperature reached 100.4° F. or higher on any two postoperative days, exclusive of the day of operation, the temperature having been taken 4 times daily. This standard has previously been used by Osoba as well as by several other authors<sup>2-5</sup> studying the general posthysterectomy morbidity. Other standards have been suggested, but this one, based upon the definition of puerperal morbidity given by the United States Joint Committee on Maternal Welfare, although somewhat severe, seems most acceptable. It will lend itself more readily to establishment as a much needed measure of surgical morbidity since it is based on an already accepted standard.

## Results

**The cone-hysterectomy group.** Of 66 consecutive patients who had a cold knife cone biopsy of the cervix followed 1 to 120 days

**Table I.** Race and cone-hysterectomy febrile morbidity

Race	No. of patients	No. morbid
White	58	23 (39.7%)
Negro	8	5 (62.5%)
Total	66	28 (42.4%)

**Table II.** Presenting complaint and cone-hysterectomy febrile morbidity

	No. of patients	No. morbid
Postcoital bleeding	11	5
Leukorrhea	8	3
Intermenstrual bleeding	23	8
Postmenopausal bleeding	7	5
Menorrhagia	1	1
Menometrorrhagia	4	2
Prolapse	1	0
Lower abdominal pain	3	1
Routine pelvic examination	8	3
Total	66	28

**Table III.** Appearance of cervix at first examination and cone-hysterectomy febrile morbidity

<i>Appearance of cervix</i>	<i>No. of patients</i>	<i>No. morbid</i>
Clean	25	10
Erosion	29	14
Lacerations	4	2
Polyp	2	0
Hypertrophy	6	2
Total	66	28

**Table IV.** The cone-hysterectomy interval and cone-hysterectomy febrile morbidity\*

<i>Cone-hysterectomy interval (days)</i>	<i>No. of patients</i>	<i>No. morbid</i>	<i>%</i>
Up to 7	15	8	53.3
8-14	11	4	36.4
15-28	21	9*	42.9
29-42	9	4	44.4
43-120	10	3	30.0
Total	66	28	42.4

\*Although there is a significant difference at the 5 per cent level in morbidity of the 15 to 28 day group as compared with the 8 to 14 day group, because of the small size of each sample it is felt that no specific conclusion should be drawn from this.

later by a total hysterectomy, 28 showed posthysterectomy febrile morbidity (42.4 per cent). There were no deaths in this group.

**Age.** The age distribution for the 66 patients in this group was from 21 to 77 years. Both the youngest and the oldest had carcinoma in situ of the cervix at the time of cone biopsy. The mean age was 44 years, the median age 43, and the mode 47 years. No relationship could be found between age and the posthysterectomy febrile morbidity rate; 14 of the patients were older and 14 were younger than the median age.

**Race.** A true ethnic distinction was not made, the patients being classed as white (58) or Negro (8). Among the white group were two Latin-American women, neither of whom showed morbidity. The febrile morbidity was apparently higher among the Negroes but their number was so small that no valid conclusion on the racial influence can be drawn (Table I). It is interesting to note that at our institution relatively fewer

Negro women are seen with preinvasive cervical carcinoma than with the invasive variety. This may be due not so much to a racial factor as to the generally poorer socioeconomic conditions under which these women live.

**Gravidity and parity.** Six of these patients were nulligravid and 7 nulliparous. The maximum gravidity was 14 and the maximum parity 11. The mean gravidity was 4.1 in the whole group as against 4.2 in the morbid patients. The mean parity was 3.3 in the whole group as against 3.4 in the morbid patients. After careful consideration of these patients, no relationship was found between previous pregnancies and the cone-hysterectomy febrile morbidity.

**Presenting complaints.** In 20 of the 66 patients no abnormal bleeding had occurred, 8 of the in situ lesions being found on routine physical examination (Table II). No relationship was found between the presenting complaint and the cone-hysterectomy febrile morbidity.

**Appearance of the cervix.** The appearance of the cervix on speculum examination varied from normality to gross hypertrophy (Table III). No relationship could be found between the appearance of the cervix or the degree of cervicitis and the cone-hysterectomy febrile morbidity.

**The cone-hysterectomy interval.** This varied from one day to 120 days and the febrile morbidity is given in Table IV. On the basis of the 66 cases studied here, there is no statistical justification for accepting a particular cone-hysterectomy interval as optimal between 1 and 120 days.

**Operative procedures.** In the cone-hysterectomy series there were 14 vaginal and 52 abdominal procedures with no significant difference in febrile morbidity. On comparative analysis as to the cause of morbidity, it was found that urinary infections were a relatively more common cause in women who had had a vaginal hysterectomy. This was probably due to the increased use of self-retaining catheters in these women, especially where cystocele repair had also been carried out. Appendectomy was performed



**Table V.** Operative procedure and cone-hysterectomy febrile morbidity

Operation	No. of operations	No. of morbid patients
Total abdominal hysterectomy	4	3
Total abdominal hysterectomy and appendectomy	11	3
Total abdominal hysterectomy and unilateral salpingo-oophorectomy	6	3
Total abdominal hysterectomy and unilateral salpingo-oophorectomy and appendectomy	9	4
Total abdominal hysterectomy and bilateral salpingo-oophorectomy	10	5
Total abdominal hysterectomy and bilateral salpingo-oophorectomy and appendectomy	9	3
Total abdominal hysterectomy and bilateral salpingo-oophorectomy and repair of cecocolic fistula	1	1
Total abdominal hysterectomy and bilateral salpingo-oophorectomy and inguinal hernia	1	1
Total abdominal hysterectomy and unilateral salpingo-oophorectomy and simple vulvectomy	1	0
Total vaginal hysterectomy	2	0
Total vaginal hysterectomy and repair	12	5
Total	66	28

in 29 patients and, of these, 10 were morbid.

In general, there appeared to be no relationship between associated operative procedures and the cone-hysterectomy febrile morbidity (Table V).

**Prophylactic antibiotics.** Prophylactic antibiotics were given to 26 patients in the cone-hysterectomy series (Table VI). The giving of prophylactic antibiotics did not reduce the febrile morbidity in this series.

**Menstrual phase at the time of hysterectomy.** In this series of patients 16 had proliferative, 13 had secretory, 14 had hyperplastic, and 23 had atrophic endometrium. No relationship between the phase of the menstrual cycle or even the stage of reproductive life and the cone-hysterectomy morbidity could be found (Table VII).

**Pathological findings in the hysterectomy specimen.** As far as possible, this was compared with the cone-hysterectomy morbidity. In 20 patients of the series in whom it was felt that the presence of residual carcinoma was unlikely, by virtue of the examination of subserial sections of the cone biopsy specimen, the uterus had been retained for special study, and the final report was not available (Table VIII). No relationship between the residual pathological findings and the posthysterectomy febrile morbidity could be established.

**The causes of febrile morbidity.** These are given in Table IX. Although pelvic infection (parametritis) with the danger of septicemia is usually considered to be the main cause of morbidity, it apparently played an important part in only one of the 28 morbid patients. The importance of postoperative parametritis is difficult to assess by clinical or laboratory methods. Urinary tract infection (pyelonephritis) appeared to be the most important cause of febrile morbidity in this series.

**Postoperative hospital stay.** The postoperative hospital stay in the cone-hysterectomy series of 66 patients ranged from 6 to 19 days with a mean stay of 9.8 days.

Among the 38 afebrile patients the mean postoperative stay was 9.2 days. Among the 28 morbid patients the postoperative stay ranged from 7 to 19 days with a mean stay of 10.6 days. The mean number of days of

**Table VI.** Prophylactic antibiotics and cone-hysterectomy febrile morbidity

Prophylactic antibiotic	No. of patients	No. of morbid patients
Combiotic	16	6
Achromycin	7	4
Distycin	1	1
Sigmamycin	1	1
Neomycin and Combiotic*	1	1
	26	13 (50%)
None	40	15 (37.5%)
Total	66	28 (42.4%)

\*This patient had a cecocolic fistula and was given this preparation pre- and postoperatively.

Table VII. Menstrual phase and cone-hysterectomy morbidity\*

	<i>Proliferative</i>	<i>Secretory</i>	<i>Atrophic</i>	<i>Hyperplastic</i>
Types of endometrium	16	13	23	14
No. of patients morbid	6	6	12	4
Per cent morbid	37.5%	46.2%	52.2%	28.6%

\*In entire series 28 of 66 patients were morbid, i.e., 42.4 per cent.

morbidity was 3 but these patients spent only 1.4 days longer in the hospital than those who remained afebrile postoperatively.

Thus, it would appear that even in the presence of morbidity the postoperative hospitalization of the patient undergoing cone biopsy followed by hysterectomy is not significantly prolonged.

**The hysterectomy control group.** Studied in this group were 62 consecutive patients who had total hysterectomies performed for benign disease. Of these, 11 patients had vaginal and 51 abdominal hysterectomy. The febrile morbidity was apparently higher in the cases of vaginal hysterectomy, but in view of the small number of cases involved, this cannot be held statistically significant. Of the 25 patients in whom incidental appendectomy was performed, only one showed morbidity.

In the entire group were 9 morbid patients giving a febrile morbidity rate of 14.5 per cent. The causes of febrile morbidity in this group are shown in Table X. Although the group is small, the reported morbidity is similar to that in several large series reported recently.<sup>6, 7</sup>

The postoperative hospital stay in these patients ranged from 6 to 19 days. The mean postoperative stay was 9.5 days for the whole group, 11.1 days for the 9 morbid patients, and 9.3 days for the 53 afebrile patients. Thus, the mean prolongation of stay among the morbid patients was 1.8 days.

**The cervical cone biopsy group.** As a further check on the validity of the concept that cone-hysterectomy morbidity was increased, a series of 69 consecutive patients who had a cone biopsy performed over the same period was studied. Eight of these women (11.6 per cent) showed postconization febrile morbidity (Table XI).

In addition to the 4 patients with severe bleeding, 6 women had mild to moderate vaginal bleeding requiring vaginal packing and supportive measures. We have no reason to believe that this is unusual since Boyd<sup>8</sup> reported "significant complications" in 20 per cent of his patients.

# Comment

In Group A there were 66 consecutive patients who had had a total hysterectomy performed within 4 months of cervical cone biopsy. There were no deaths but the febrile mortality was found to be 42.4 per cent. In

Table VIII. Pathological findings in hysterectomy specimen and cone-hysterectomy morbidity

<i>Lesion</i>	<i>No. of patients</i>	<i>No. morbid</i>
Carcinoma in situ of cervix	17	9
Atypical hyperplasia of cervix	4	1
Chronic cervicitis	22	5
Very early invasive carcinoma	3	2
Unknown (uterus retained for special studies)	20	11
Total	66	28

Table IX. Causes of febrile morbidity in 66 postoperative cone-hysterectomy cases

<i>Cause</i>	<i>No. of morbid patients</i>
Urinary tract infection	17
Urinary tract infection and allergic reaction to blood transfusion	1
Parametritis and pelvic peritonitis with ileus	1
Abdominal wound infection	2
Abdominal wound infection and pelvic hematoma	3
Pneumonia	2
Cecostigmoid bowel fistula	1
Pyrexia of unknown origin	1
Total	28

**Table X.** Causes of posthysterectomy febrile morbidity in group of 62 consecutive hysterectomy patients

<i>Cause</i>	<i>No. of patients</i>	<i>Total</i>
<i>Abdominal</i>		
Pneumonia	2	
Hematoma of vaginal cuff	1	
Abdominal wound infection	1	
Urinary infection	1	
Unknown	1	51
<i>Vaginal</i>		
Urinary infection	3	11
<b>Total</b>	<b>9</b>	<b>62</b>

this group, factors such as age, gravidity, parity, the presenting complaint, the appearance of the cervix, the type of operation, the performance of associated operative procedures, the use of prophylactic antibiotics, the menstrual phase at the time of hysterectomy, and the residual cervical pathological findings appeared to have no effect on the posthysterectomy morbidity.

When the cone-hysterectomy time interval was considered, the morbidity for the small number of cases under 8 days (15 patients) appeared increased. Statistical evaluation showed that this could have been accounted for on the basis of chance. Furthermore, consideration of the 69 patients in the cone biopsy group revealed that conization per se was associated with a morbidity rate of 11.6 per cent. Since most of the postoperative complications of cone biopsy occur within the first week, it seems that little will

be gained by avoiding the hysterectomy during this period and performing the operation between the eighth and the forty-second day. The mean febrile morbidity for a cone-hysterectomy interval under 6 weeks was 44.6 per cent, whereas between 6 weeks and 4 months it was 30 per cent. Again, this difference is not statistically significant but it seems reasonable to suppose that with a longer cone-hysterectomy interval the morbidity should approach that for the hysterectomy control series (14.5 per cent).

In the presence of the almost universal problem of bed shortage, the postoperative hospital stay is an important factor. It also provides a means of assessing the significance of the postoperative morbidity, and for this reason it was noted in each of the groups studied.

The postoperative stay of the patients in the cone-hysterectomy (A) and hysterectomy (B) groups was not significantly different, being 9.5 days and 9.8 days, respectively. The range of hospitalization was the same in both groups, that is, 6 to 19 days. The mean postoperative stay in the cases of morbidity was approximately the same in both groups, being 10.6 and 11.1 days, respectively. The mean number of febrile days in the morbid patients in each group was 3.

As a result of this study, we believe that in a patient with a cone-hysterectomy interval of less than 6 weeks the postoperative febrile morbidity may be increased although statistical evaluation indicates that the increase could be accounted for on the basis

**Table XI.** Postconization. Febrile morbidity in 69 cases

	<i>Postoperative day</i>	<i>Action required</i>	<i>No. of patients*</i>
Severe postoperative bleeding; temperature over 100.4° on any 2 postoperative days	Seventh	Transfusion; laparotomy revealed hematoma below the vesicouterine fold of peritoneum	2
	Eighth	Vaginal packing and transfusion; suturing of cervix controlled bleeding	1
	Third	Vaginal hysterectomy	1
Febrile response from urinary tract infection	First to eighth	Sulfonamides or antibiotics	4

\*Total patients morbid, 8 (11.6 per cent).



of chance. Even if there is an increase, however, this does not appear to represent a serious situation when related to the patient's postoperative hospital stay, and it would appear that the problem has been magnified by the application of a severe, although none the less acceptable, standard of postoperative morbidity. Thus, it would appear that if the hysterectomy is not postponed for 6 weeks, it matters little when it is performed within that period. When it is felt that a hysterectomy is an urgent necessity and when the patient may not return for follow-up, the gynecologist should perform a hysterectomy as soon as the cone biopsy report is available. It would appear that this practice will place the patient in little jeopardy.

It has been considered that the performance of a hysterectomy for cervical carcinoma in situ within 24 hours of the cone biopsy will reduce the hysterectomy morbidity, avoid postconization complications, and reduce the patient's hospital stay. This possibility is being investigated at present at our institution by means of a new "rapid blocking" histological method. The advantages of reducing the cone-hysterectomy interval to 24 hours, however, may well be outweighed by such factors as: (a) subjecting the patient to two anesthetics within 24 hours, and (b) overhurried and therefore less reliable histopathological examination of the cone biopsy specimen.

Careful examination of the cone biopsy specimen is essential before hysterectomy is performed for intraepithelial carcinoma of the cervix. If possible, at least 12 blocks should be made of a cone biopsy specimen with 3 slides being made from each block. Indeed, we feel that adequate histopatho-

logical examination of the cone biopsy specimen is more important to the patient than the cone-hysterectomy interval.

### Summary

1. A series of 66 consecutive patients who had had a total hysterectomy within 4 months of a cone biopsy of the cervix was studied. There were no deaths, but a febrile morbidity of 42.4 per cent was found.

2. This was increased as compared with a hysterectomy control group of 62 patients who showed a postoperative febrile morbidity of 14.5 per cent.

3. The only factor which appeared to be associated to some degree with the post-hysterectomy febrile morbidity was the cone-hysterectomy time interval, but statistical evaluation suggested that this could be explained on the basis of chance. The febrile morbidity was not significantly high even with an interval of less than 8 days and, furthermore, this would be offset by the avoidance of the postconization morbidity expected within this period.

4. When the hysterectomy was performed within 6 weeks of cone biopsy the mean morbidity was 44.6 per cent, falling to 30 per cent in the small number of cases in which a hysterectomy was performed 6 weeks to 4 months after cone biopsy.

5. There was no increased morbidity in the cone-hysterectomy group when related to postoperative hospital stay as compared with the control hysterectomy series.

6. It is concluded that, while the febrile morbidity may be increased when hysterectomy is performed within 6 weeks of cervical cone biopsy, no conclusive evidence for this could be found. Even if increased, it is apparently not a serious problem.

### REFERENCES

1. Osoba, D.: *Canad. M. A. J.* 79: 805, 1958.
2. Smith, P. H.: *AM. J. OBST. & GYNEC.* 40: 118, 1940.
3. Jones, H. O., and Doyle, L. W., Jr.: *AM. J. OBST. & GYNEC.* 46: 160, 1943.
4. Danforth, W. C.: *AM. J. OBST. & GYNEC.* 52: 218, 1946.
5. Pratt, J. H., Lee, M. J., Hasskarl, W. F., Jr., and Brandes, R. W.: *AM. J. OBST. & GYNEC.* 61: 407, 1951.
6. Watts, W. F., and Kimbrough, R. A., Jr.: *Obst. & Gynec.* 7: 483, 1956.
7. Schneider, G. T., and Weed, J. C.: *South. M. J.* 51: 561, 1958.
8. Boyd, J. R.: *AM. J. OBST. & GYNEC.* 75: 983, 1958.

# Surgical investigation of the cervix with the trachelotome

FRANK C. SPENCER, M.D.

RALPH C. BENSON, M.D.

*Honolulu, Hawaii*

CONIZATION is the only technique which will consistently determine the presence and character of most small occult cervical cancers. It is likewise true that post-operative bleeding is a principal complication of the operation. Nevertheless, excellent conization and the limitation of bleeding is possible with the use of the trachelotome. This type of cervical conization is superior to punch or wedge biopsy; it is coming into frequent use.

This is a study of conization of the cervix at the Kapiolani Maternity and Gynecological Hospital from the time of inception of the Spencer trachelotome<sup>1-3</sup> Jan. 1, 1955, through Oct. 18, 1958. The trachelotome is compared with other instruments for efficiency in this surgical procedure.

## Material and methods

Conizations of the cervix numbering 272 were performed by 35 different physicians, 11 of whom were obstetricians-gynecologists. The trachelotome was used in 147 of the operations; the scalpel in 113, and the punch biopsy instrument in 12.

## Improved trachelotome technique

The present technique for use of the trachelotome is an advance over the previous method.

The blade of the instrument is flash-sterilized because the razor edge will not with-

stand autoclaving or prolonged soaking in antiseptic solutions.

The cervix is seized at the anterior lip with a double-toothed vulsellum forceps. The fundus is sounded and the cervix is dilated to a size 20 French. A Lilly forceps is inserted to remove polypi, and curettage of the fundus is accomplished. Following curettage, the cervix is grasped at 9 and 3 o'clock with a single-toothed tenaculum about 1 cm. from the dilated os. The forceps on the anterior lip is removed. Lateral placement of the instruments stabilizes the cervix, draws it downward, and obviates insertion of lateral vaginal retractors.

From an anterior starting point, the cervical canal is completely circumscribed with slow, deliberate, short cutting strokes. The surgeon's left hand holds the trachelotome firmly against the cervix; the right hand is free to rotate the instrument within the lumen. A thin, continuous strip of tissue is obtained from the mucosquamous junction to the internal os. All tissue removed is collected within the instrument. Next, conization is completed with the removal of any surface tissue missed in notches or lacerations; the trachelotome is then removed.

Cotton Oxycel impregnated with powdered sulfanilamide is then placed against the cut surface. The tenacula are removed and the Oxycel is secured by firm vaginal packing. Cotton Oxycel is more hemostatic and remains applied better than Gelfoam.

The trachelotome is dismantled and the tissue which is contained within it is spread

*From the Kapiolani Maternity and  
Gynecological Hospital.*

on a blotter to prevent curling of the specimen and to allow orientation of the strips by the pathologist. It is then placed in a fixative solution.

The patient is allowed out of bed upon recovery from the Pentothal Sodium anesthetic, and is usually discharged from the hospital within 24 hours. Two days after operation, the packing is removed in the office or clinic, and the vagina is lightly repacked with gauze. Adherent cotton Oxycel should *not* be peeled away because this may cause bleeding. The patient is instructed to remove the gauze the next day. Upon re-examination in from 2 to 3 weeks, the cervix is usually found to be well healed and without evidence of infection.

#### Indications

The reasons for surgical conization in this series are described in Table I.

It must be assumed that hospital records listed several indications in various combinations. For instance, some patients with a diagnosis of cervicitis probably also had suspicious smears, but the hospital charts lacked this information.

#### Results

Definitive pathology findings included 35 so-called precancerous conditions (Table II).

Carcinoma in situ indicates microscopic lesions of malignant cells which are noninvasive. There are other patterns in this category in which malignant cells are seen to plug glands, but without penetrations of the "basement membrane." Thirty-five cases of carcinoma in situ as well as 11 frankly invasive malignant lesions are detailed in Table III.

Hemostasis at the time of conization was achieved with point sutures and packing (Table IV).

Twenty-six patients returned to the hospital because of complications. Hemorrhage was the reason for the readmission of 25 patients. The method used to control bleeding and the transfusions administered are shown in Table V.

Only one readmission was necessitated by

**Table I.** Indications for surgical conization

Cervicitis	171
Abnormal uterine bleeding	122
Papanicolaou smear, Class III or IV	81
Cervical polyp	10

**Table II.** Possibly precancerous conditions

Atypical epidermization	15
Dyskeratosis	11
Basal cell hyperplasia	6
Atypical metaplasia	3
Total	35

**Table III.** Proved malignant lesions

Carcinoma in situ	35
Obviously invasive carcinoma	5
Microinvasive carcinoma	3
Adenocarcinoma	3
Total	46

**Table IV.** Hemostasis for conization

Cotton Oxycel with vaginal packing	112
Absorbable sutures	68
Vaginal packing only	42
Gelfoam with vaginal packing	36

**Table V.** Readmission to hospital for treatment of hemorrhage

	Scalpel (14)	Trachelotome (11)
Resuture	8	2
Packing only	6	9
Transfusion	3	2

**Table VI.** Disposition of cases of carcinoma in situ

Total hysterectomy; negative cytology	28
Lost to follow-up	3
Sturmdorf tracheloplasty; 2 pregnancies; negative cytology	1
Diagnosis debated; no subsequent treatment; negative cytology	1
Trachelotome only; negative cytology	1
Trachelotome only; "stroke"; definitive treatment deferred; positive cytology	1
Total	35



infection—a case of metritis and parametritis which occurred 28 days after scalpel conization. This complication was brought under control by antibiotic therapy within 10 days of hospitalization.

Electrocoagulation was not used for hemostatic effect or to “seal tissue” in any case.

Hysterectomy, when indicated, was carried out in most instances promptly after the pathologist's report on tissue removed by conization.

Of the 113 patients whose cervixes were conized with the scalpel, 4 had a major second operation within 10 to 28 days. There was a 6½ month delay in one instance. The longest postoperative hospitalization was 9 days.

When cancer was detected in tissue removed by the trachelotome, the earliest subsequent operation followed in 3 days. In 2 cases, there was a 3-month delay. Hospitalization was not prolonged. The shortest interval was 5 days; the longest, 15 days in a patient who developed ileus. We could not relate complications to the time of the second phase of operation following conization with either method.

#### Treatment of malignant cervical lesions

Forty-six cases of malignant disease of the cervix were treated. The five cases of definitely invasive squamous cell carcinoma were treated by irradiation. One was treated with colloidal gold and radium, and the other 4 with radium and x-ray irradiation. Three cases of microscopically invasive cancer were treated as follows: one by irradiation and 2 by total hysterectomy. In the 2 cases treated by hysterectomy, only residual carcinoma in situ was found in the specimens; no micro-invasion was seen.

The ultimate disposition of the 35 cases of in situ carcinoma is described in Table VI. In these cases, the trachelotome was the instrument used 28 times, the scalpel 5, and the punch biopsy forceps 2 times. Residual malignant disease in cases of carcinoma in situ was detected in the specimen after total hysterectomy in 29 instances. This is outlined in Table VII.

**Table VII.** Carcinoma in situ, conization, hysterectomy—residual cancer

Detected by trachelotome		22
Residual cancer found	15	
No residual cancer	7	
Detected by scalpel		5
Residual cancer found	3	
No residual cancer	2	
Detected by punch biopsy		2
Residual cancer	2	
Total		29

#### Comment

A Cytology Laboratory<sup>4-7</sup> has been maintained by the Hawaii Cancer Society for the past 10 years. Any doctor may send smears to this facility without charge. This diagnostic service, together with that of private laboratories and the outpatient department of the numerous Hawaiian hospitals, gives our community a very broad cytologic coverage. In 1958, the number of cervical smears read was equivalent to one out of 5 women in the Island population. The result of the work of these laboratories increased the number of cases in which surgical conization of the cervix was required. The diagnosis of early cancer was expedited; this is genuine progress.

A conization should be performed at the time of a diagnostic curettement. Thus, “pre-cancerous” and early malignant lesions of the cervix may also be discovered. Incidentally, chronic cervicitis will often resolve after conization when better drainage of cervical mucus is established.

The thin tissue strips representing the entire trachelotome specimen can be embedded in 2 or 3 paraffin blocks, yielding an average of 15 to 20 separate strips of tissue. With the usual deep scalpel cone, a generous sample of tissue cannot be obtained without unnecessary hazard from bleeding and infection.

Conization should not be utilized as definitive therapy for carcinoma in situ, however. Debatable cases must be followed closely by vaginal cytology and repeat conization. More radical therapy may be required subsequently if carcinoma persists or recurs.

Electrocoagulation destroys much tissue,

encourages infection, causes scarring and stenosis at the internal os, and often results in secondary hemorrhage.

Hysterectomy can be accomplished soon after conization without significant increase in postoperative complications or extension of hospitalization.

Serious late bleeding resulted in 12.4 per cent of cervixes conized with the scalpel. Trachelotome conization of the cervix is also occasionally followed by bleeding complications, but, in the cases studied, delayed hemorrhage occurred in only 7.5 per cent of patients in whom the trachelotome was used. We have found that this can be reduced further by nonabsorbable, deep mattress hemostatic sutures in the cervix. After the sutures are tied, the ends are left about 2 inches long. These strands can then be readily identified and removed in 3 weeks, after the likelihood of postoperative bleeding has passed.

The trachelotome is not a difficult instru-

ment to use, and complications are not common. An excellent specimen is obtained and in a better form than that produced by the scalpel. A wide sampling is obtained of tissue from the internal to the external cervical os.

#### Summary and conclusions

Two hundred seventy-two surgical conizations of the cervix have been reviewed, representing a 3 year, 10 month experience at the Kapiolani Maternity and Gynecological Hospital, Honolulu. The instruments used, indications, pathologic findings, complications, and ultimate success of therapy of patients with neoplasia are presented. An improved technique of the use of the trachelotome is offered and its rationale is discussed.

We are grateful to the members of the staff of Kapiolani Maternity and Gynecological Hospital for their interest and cooperation.

---

#### REFERENCES

1. Spencer, Frank C.: *AM. J. OBST. & GYNEC.* 70: 447, 1955.
2. Read, Charles D., Jr.: *J. Obst. & Gynaec. Brit. Emp.* 62: 796, 1955.
3. Emerson, R. G.: *Brit. M. J.* 5056: 1284, 1958.
4. Spencer, Frank C.: *Hawaii M. J.* 10: 437, 1951.
5. Quisenberry, Walter B.: *Proceedings of the Third National Cancer Conference, Philadelphia, 1957*, J. B. Lippincott Company.
6. Quisenberry, Walter B.: *Postgrad. Med.* 21: 179, 1957.
7. Quisenberry, Walter B.: *Hawaii M. J.* 17: 233, 1958.

# Primary carcinoma of the Fallopian tube

## Report of a case

PAUL D. MOZLEY, LIEUTENANT (MC) USN

WILLIAM S. BAKER, JR., CAPTAIN (MC) USN

*San Diego, California*

PRIMARY carcinoma of the Fallopian tube is a rather infrequently reported gynecologic oddity with just under 600 cases described in the literature since 1888.<sup>1</sup> It purportedly occurs once in every one thousand gynecologic admissions; is discovered in 0.3 per cent of all gynecologic laparotomies; and accounts for 0.5 per cent of all malignant growths in the genitals.<sup>2</sup> Improper or inadequate treatment is occasionally instituted at the time of laparotomy simply because the true character of a pelvic mass is not recognized, thus contributing unwittingly to a very poor prognosis.<sup>3</sup>

The diagnosis is usually not made prior to laparotomy.<sup>3</sup> Falk has established the diagnosis from cul-de-sac aspiration and the examination of the "spun down" fluid with cytologic methods. Brewer and Guderian<sup>4</sup> and Larsson and Schooley<sup>5</sup> have successfully diagnosed this entity by vaginal cytologic examination. A negative curettage following a positive vaginal smear that persists is strong indirect evidence of a possible primary or metastatic tubal cancer. Pancreatic carcinoma has been reported as metastasizing to the tube.<sup>4</sup>

The infrequent occurrence of this tumor fosters controversy concerning its proper treatment. Mason<sup>1</sup> and Rhu<sup>6</sup> recommend bilateral pelvic lymphadenectomy and removal of all visible metastatic tumor after pan-

hysterectomy and bilateral salpingo-oophorectomy. Others do not feel this procedure is justified. Postoperative irradiation is of dubious value but is generally recommended. Block<sup>7</sup> has suggested leaving the uterus in situ as a radium carrier, and Engström<sup>8</sup> utilized radium in the uterus and vagina in his recently reported series of cases. His exceptionally good results would seem to endorse favorably this method of management.

The case report to follow is a rather typical example of primary cancer of the tube in which the diagnosis was considered as a strong possibility prior to operation. We were thus able to photograph the lesion in situ, and it is for this reason plus the hope that we may stimulate awareness of this disease that we are making this report.

A. A., a 60-year-old white woman, gravida ii, para ii, was admitted to the United States Naval Hospital, San Diego, California, on Dec. 5, 1956, because of postmenopausal vaginal spotting of 6 months' duration. Physical examination was essentially negative except for a slightly enlarged uterus. Passage of a sound resulted in release of about 250 c.c. of purulent exudate from the endometrial cavity. Penicillin and streptomycin therapy was maintained for 14 days and was followed by dilatation and curettage. The patient remained afebrile and essentially symptom-free and was discharged on Dec. 22, 1956, with a diagnosis of acute endometritis confirmed by microscopic examination of the curettings.

A few weeks after discharge from the hospital the patient noted the appearance of a clear, straw-colored, sticky, odorless vaginal discharge plus a low backache. These aggravating symptoms were tolerated by the patient until October,

*From the Obstetrical and Gynecological Service, United States Naval Hospital.*

*This work is not to be construed as necessarily reflecting the views of the Department of the Navy.*





Fig. 1. Photograph of the tube in situ at operation.

1957, when she was again admitted to the hospital. Pelvic examination at that time revealed an atrophic, clean cervix with a clear, straw-colored, sticky, odorless liquid literally dripping from the external os. The corpus was small, regular, and smooth, and the adnexa were normal. Endometrial biopsy produced no tissue for examination. Intravenous pyelography and cystoscopy revealed a normal upper and lower urinary tract. Barium enema and sigmoidoscopy revealed a normal lower gastrointestinal tract. X-ray findings in the chest were normal. Cultures of the vaginal discharge were repeatedly negative, and the Papanicolaou smear was reported as Class I.

On Oct. 31, 1957, a repeat curettage was performed and only scanty tissue was obtained which was insufficient for pathologic diagnosis and which failed to grow any organisms when cultured. A careful pelvic examination at this time was reported as normal. A cell block on the collected fluid discharge was reported as negative for malignant cells. Ureterouterine and vesicouterine fistulas were carefully ruled out by the performance of dye excretion tests. The patient was then discharged to the outpatient clinic but continued to complain of the low back pain and watery vaginal discharge until she was readmitted to the hospital for an exploratory laparot-

omy on Feb. 9, 1958. Complete physical examination at this time revealed no abnormalities. On pelvic examination, a 2 to 3 cm. firm, nontender, mobile left adnexal mass was detected. A preoperative diagnosis of uteroperitoneal fistula or carcinoma of the corpus uteri or Fallopian tube was strongly entertained.

At operation on Feb. 10, 1958, there was noted a shrimp tail-shaped, 3 by 5 cm., spongy mass completely replacing the left Fallopian tube (Fig. 1). This mass on cut surface resembled spoiled fish flesh. Panhysterectomy and bilateral salpingo-oophorectomy were carried out without incident. The omentum, liver, and other abdominal structures were not involved grossly in the pathologic process. A frozen section diagnosis of primary adenocarcinoma of the left Fallopian tube was made at the time of operation and this was later confirmed on examination of the paraffin sections (Fig. 2). Before the abdomen was closed, an 18 gauge polyethylene tube was placed in the pelvis and one end was brought out through a stab wound in the flank. On the fifth postoperative day 100 mc. of radioactive colloidal gold was instilled through this tube and the tube removed after 100 hours. The post-

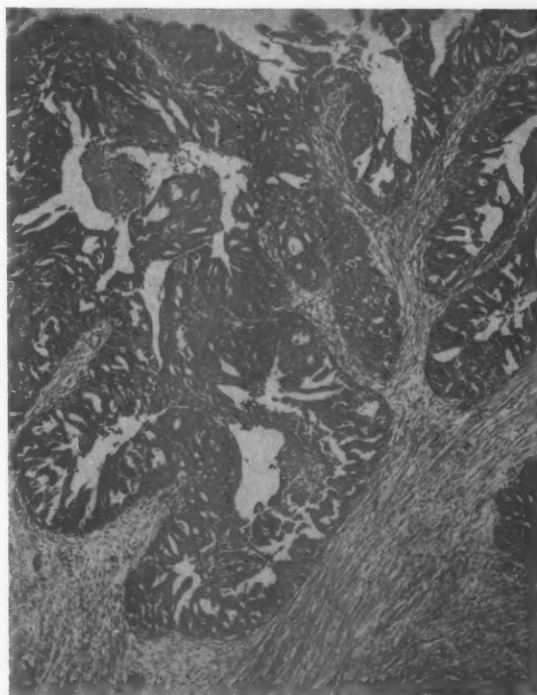


Fig. 2. Microscopic section of tumor showing adenomatous pattern. (A.F.I.P. photo.  $\times 50$ ; reduced  $\frac{1}{5}$ .)

operative course was uneventful. It was recommended by the Gynecology Tumor Board that no irradiation therapy be given at this time and the patient was closely followed in the outpatient tumor clinic.

In October, 1958, a palpable left supraclavicular node was detected and on biopsy examination on Nov. 3, 1958, it was noted to contain metastatic adenocarcinoma. The patient received cobalt<sup>60</sup> therapy to the left supraclavicular area and was fairly comfortable for the next 3 months. After completion of the cobalt<sup>60</sup> therapy the patient was again admitted to the hospital because of upper respiratory difficulty, and x-ray examination of the chest revealed the presence of metastatic disease in the lungs. The condition of the patient progressively deteriorated over the

next several weeks and she died on March 18, 1959.

Necropsy revealed metastatic disease in the pericardium, lungs, retroperitoneal lymph nodes, colon, kidneys, bladder, vagina, left adrenal gland, and sternum.

#### Summary and conclusion

1. A typical case report of primary carcinoma of the Fallopian tube has been presented along with a photograph of the lesion taken in situ at the time of operation.

2. Improper or inadequate treatment of this tumor may be avoided if it is recognized as such at the time of laparotomy.

---

#### REFERENCES

1. Mason, L. W.: *Am. J. Surg.* 93: 842, 1957.
2. Kamholz, J. H.: *Clin. Proc. Jewish Hosp. Philadelphia* 3: 87, 1950.
3. Johnson, W. O.: *Am. Surgeon* 24: 489, 1958.
4. Brewer, J. I., and Guderian, A. M.: *Obst. & Gynec.* 8: 664, 1956.
5. Larsson, E., and Schooley, J. L.: *AM. J. OBST. & GYNEC.* 72: 1364, 1956.
6. Rhu, H. S.: *Obst. & Gynec.* 9: 355, 1957.
7. Block, E.: *Acta radiol.* 28: 49, 1947.
8. Engström, L.: *Acta obst. et gynec. scandinav.* 36: 289, 1957; *Obst. & Gynec. Surv.* 13: 431, 1958.

# Primary carcinoma of the uterine tube

## Report of an unusual case

J. W. RODDICK, JR., M.D.

D. N. DANFORTH, M.D.

*Evanston, Illinois*

IN THE files of the Evanston Hospital, 3 cases of primary tubal carcinoma are recorded. One of these patients is living 3 years after operation and external irradiation, but her condition is much deteriorated as the result of proved cerebral metastases. The second patient had a vaginal vault recurrence 4 years after operation and external irradiation and now, 2 years later, is living without evidence of disease. The third, the subject of this report, was recently operated upon for what was either a metastatic lesion or a second primary tumor of the contralateral tube some 12 years following the original operation.

Adenocarcinoma of the uterine tube occurs in from 0.16 to 1.6 per cent of primary genital cancers, depending upon the series quoted. The mortality rate is notoriously high, few cases with a 5 year survival being reported. The long survival of this patient, her excellent health in the meantime, and the ultimate appearance of a second tubal carcinoma many years later are features which are sufficiently unusual to make this case of particular interest.

### Case report

The patient was a white woman, gravida iii, para iii, who was first admitted to the Evanston Hospital at the age of 42 on Sept. 25, 1947, with the chief complaint of vaginal bleeding for

3 months. She stated that she had had normal periods until 6 months prior to admission when they became irregular. For the 3 months prior to admission she had had almost continuous vaginal bleeding and intermittent pinkish-yellow discharge, but no other history of abnormal bleeding, dysmenorrhea, backache, or other symptoms. The inventory of systems was negative. General examination was essentially negative. Pelvic examination disclosed a soft, fixed, slightly tender mass about 8 cm. in diameter in the right lower quadrant. Laboratory findings on admission were normal. At laparotomy on Sept. 26, 1947, "a great deal of free fluid" was immediately encountered. The uterus was normal in size. The left tube and ovary were described as normal. The right tube was very large and tortuous and contained a tumor mass which was densely adherent to the uterus and the peritoneum of the cul-de-sac. An abdominal total hysterectomy and a right salpingo-oophorectomy and appendectomy were performed.

On gross examination, the specimen was found to consist of a complete uterus and, separately, the right tube and ovary. The uterus was normal in size and shape, and the endometrium appeared normal. The right tube measured 10 cm. in length and was club-shaped. The distal end formed a large yellow rubbery mass, measuring 4 by 4 by 3 cm. The fimbriated end of the tube was lost in this mass. The mass was covered with peritoneum with numerous fibrous adherent tags. In two areas the surface appeared broken and the contents of the mass exuding. The proximal half of the tube was dark blue and the serosal surface smooth. The ovary measured 2 by 1 by 1.5 cm. and was located 2 cm. from the proximal end of the tube. The tube was filled with blood. The mass at the distal end, on section, had a finely lobulated bulging surface

*From the Department of Obstetrics and Gynecology, Northwestern University Medical School, and the Evanston Hospital.*





Fig. 1. Right tubal carcinoma, 1947. ( $\times 200$ ; reduced  $\frac{1}{4}$ .)

which was grayish yellow in color, soft, and friable. Section of the ovary showed a small corpus luteum and corpus albicans. Microscopically, the tubal plicae were thrown into multiple papillary projections lined by several layers of atypical epithelial cells which were low columnar or cuboidal in type, with heavily stained nuclei and frequent mitoses (Fig. 1). There was invasion through the muscularis. The transition from the more proximal normal tubal mucosa and the tumor was sharp. The plicae were thickened and edematous and infiltrated by moderate numbers of round cells, plasma cells, and monocytes. This inflammatory reaction was present throughout the wall of the tube. The endometrium was in the early secretory phase. The diagnosis was papillary carcinoma of the uterine tube (fimbriated end).

The postoperative course was entirely uneventful and the patient was discharged on the tenth postoperative day. External irradiation was begun on the eighth postoperative day. The total tumor dose, by means of the 250 kv. unit, was 2,340 r through each of two anterior portals and 2,496 r through each of two posterior portals.

Shortly after this patient's operation her doctor died. Therefore, there was no further known

follow-up until October, 1956, when we began to search the record room for previous cases of carcinoma of the tube. Upon discovery of this case, an effort was made to get in touch with a surviving member of the family to learn how long the patient had survived and whether an autopsy had been performed. To our surprise, the patient answered the telephone. She agreed to come into the office for an interview and for examination. She had no complaints and was in excellent general health except for slight obesity. On examination the vulva and vagina were found to be normal except for moderate relaxation. Bimanual examination revealed no masses or fixation whatsoever and no tenderness. The remaining left adnexa could not be outlined. On speculum examination the vaginal vault was healthy and well supported. The hemoglobin level was 14.8 Gm., and the urine was normal.

The patient was not seen again until March 3, 1959, at which time she complained of dyspareunia, vague lower abdominal discomfort, and a yellow discharge occasionally flecked with blood, all of which dated from November, 1958. She had been treated by a local physician with no relief. On examination, a polypoid structure (3 mm. in diameter) was found in the left vaginal vault and a lemon-sized, tender mass in the

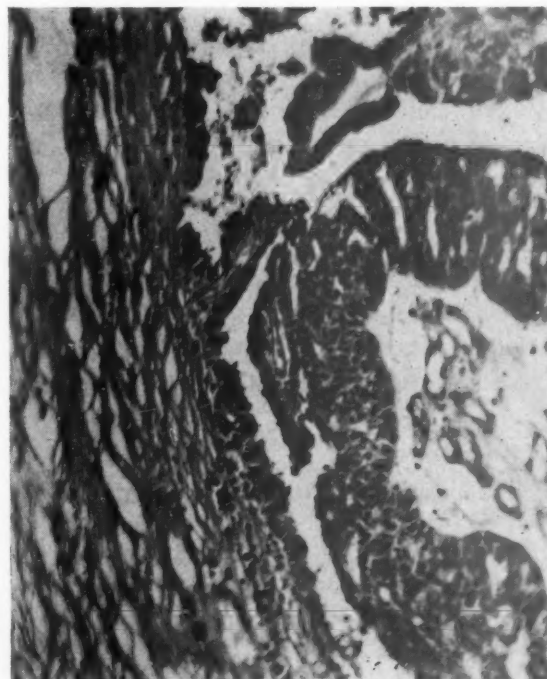


Fig. 2. Left tubal carcinoma, 1959. ( $\times 200$ ; reduced  $\frac{1}{4}$ .)

pelvis, apparently fixed to the vaginal vault at the left vaginal angle. The polypoid mass was biopsied and found to show only chronic inflammation of mucous membrane. A Papanicolaou smear was reported as negative. She was admitted to the hospital on March 4, 1959, 11½ years after her previous admission.

At this time she was 54 years old. The abdominal discomfort was described as a vague sense of fullness and pressure. Actual pain was absent, and there was no history of cramps, chills, fever, or weight loss. There was no change in the bowel habits, and there were no urinary symptoms except for occasional stress incontinence. General inventory of symptoms was negative. On abdominal examination there was direct tenderness to deep palpation of the left lower abdomen, but no spasm or rebound. The liver, spleen, and kidneys were not felt. No masses were felt. On pelvic examination there was a firm mass, 8 cm. in diameter, in the posterior cul-de-sac which was quite tender and semifixed. Proctosigmoidoscopy to 17 cm. showed the bowel to be normal; at that point, however, there was marked fixation of the sigmoid, and attempts to negotiate the angle were extremely uncomfortable to the patient and were discontinued. Chest x-ray findings were normal. Lower gastrointestinal series showed no intrinsic or extrinsic abnormalities of the colon except for a few small diverticula of the sigmoid portion. The lateral contour of a rounded soft tissue mass in the left side of the true pelvis having the approximate size of a small lemon was noted. This, however, left no definite impression on the colon. Laboratory findings were normal throughout. Because of the possibility of sigmoid involvement, bowel preparation (consisting of minimum fiber diet, succinylsulfathiazole, and neomycin) was begun on March 8, 1959.

At laparotomy, March 11, 1959, the rectosigmoid was found to be very intimately adherent to the anterosuperior, medial, and posteroinferior aspects of a left adnexal tumor measuring approximately 8 cm. in diameter. Several loops of small bowel were similarly adherent to the posterior aspect of the tumor. The anterior adhesions were divided under direct vision. The medial and posterior adhesions were divided by finger dissection and the cyst was mobilized and removed. A portion of rectosigmoid was found adherent to the medial aspect of the resected

tumor, and exploration revealed a defect in the rectosigmoid measuring about 3 cm. in diameter. A segmental resection of the sigmoid was carried out, and a primary anastomosis done. A defect in the dome of the bladder musculature was also repaired.

Examination of the specimen revealed a yellow, rounded, friable tumor which measured 7 by 5 by 3 cm. The cut surface was soft and yellow-gray with a few scattered areas of hemorrhage. Microscopically the tumor was located within the uterine tube (Fig. 2). It was composed of a large number of epithelial cells arranged in clusters or in a gland pattern which had an occasional papillary arrangement. The cells showed marked variation in size and shape. Numerous atypical mitoses were seen, as well as many areas of necrosis and hemorrhage. Similar areas of tumor were present on the surface of the ovary, but no infiltration was noted. One section showed tumor infiltration of the serosa of the colonic wall. The final diagnosis was papillary adenocarcinoma of the left uterine tube.

Operation was followed immediately by external irradiation. With the 250 kv. x-ray unit, a total tumor dose of 5,024 r was given through the same 4 portals as previously and, in addition, through one perineal portal. With the exception of a temperature of 101.8° F. on the second postoperative day, the patient's course was uneventful, and she was discharged in apparently good condition on the tenth postoperative day.

Vaginal examination 6 weeks after operation disclosed no abnormal findings, and the patient's general condition was excellent.

### Conclusions

It does seem unreasonable to suppose that a tumor of the left tube, metastatic from the original tumor of the right tube, would remain inactive for more than 10 years, especially in view of the recognized rapidity of growth of tubal carcinoma. It is also unreasonable to presume that this is a second and unrelated primary carcinoma of the contralateral uterine tube. Since it is necessary to select one or the other of these bizarre hypotheses, however, the second does appear to be rather less objectionable than the first.

# The syndrome of dysmenorrhea and unilateral gynatresia in a double uterus

Report of a case and review of the literature

GUENTHER C. MERCKEL, M.D.

MOSES C. SUCOFF, M.D.

BLANKA SENDER, M.D.

*Paterson, New Jersey*

CONGENITAL anomalies of the female genital tract arising through incomplete fusion or faulty adaptation of Müllerian ducts are fairly frequent. If all lesser forms are included, one per cent of all women exhibit such malformations.<sup>1</sup> Detailed descriptions are given in standard textbooks of embryology or pathology.<sup>2</sup> For the purpose of this presentation, it may be briefly stated that incomplete fusion of the Müllerian ducts results in division of the uterine cavity by a longitudinal septum, which may be complete or partial (uterus septus duplex, uterus subseptus), and which may be accompanied by similar division of the vagina. Faulty adaptation leads to duplication of organs or their parts, from a complete symmetrical double uterus and double vagina (uterus didelphys) to the mildest form of bicornuate uterus indicated by a barely perceptible flattening of the fundus.

These malformations seldom produce clinical symptoms except, on occasion, during pregnancy and delivery. However, if a partial or complete double uterus is accompanied by focal atresia in one lumen, sufficient to obstruct the flow of menstrual blood from that side, it may give rise to a characteristic clinical syndrome which includes: (1) unilateral pelvic tumor, (2) onset of dysmenorrhea shortly after menarche,

and (3) increasing severity of dysmenorrhea with each subsequent menstrual period.

Although unilateral atresia in a double uterus is a rare event, the syndrome is of importance because it occurs in women just entering the childbearing age. If recognized, it is amenable to conservative surgical treatment. At least 16 such cases can be found in the gynecological literature. The following case clearly illustrates the diagnostic criteria and the therapeutic results.

## Case report

A. P., a 16-year-old white girl, was admitted to the Barnert Memorial Hospital with very severe dysmenorrheic pain. There was no significant past history. The girl had had the usual childhood diseases; she had had no operations or accidents. Her appetite and activities were normal except when dysmenorrhea occurred. The patient had a tendency to constipation. The first menstrual flow occurred at the age of 12. Menses were regular, every 28 days, lasting 4 days. Approximately one year after menarche, she began to develop dysmenorrhea which was at first short in duration and moderate, and later set in one week before the menstrual flow and lasted throughout the entire bleeding interval. Various medications brought some transient relief. One year before hospitalization, the pain became very severe and grew significantly worse at each subsequent period, subsiding only for a few days in the intermenstruum. The pain was localized in the lower abdomen with definite radiation to the left side and the back.

*From the Departments of Pathology and Surgery, Barnert Memorial Hospital.*



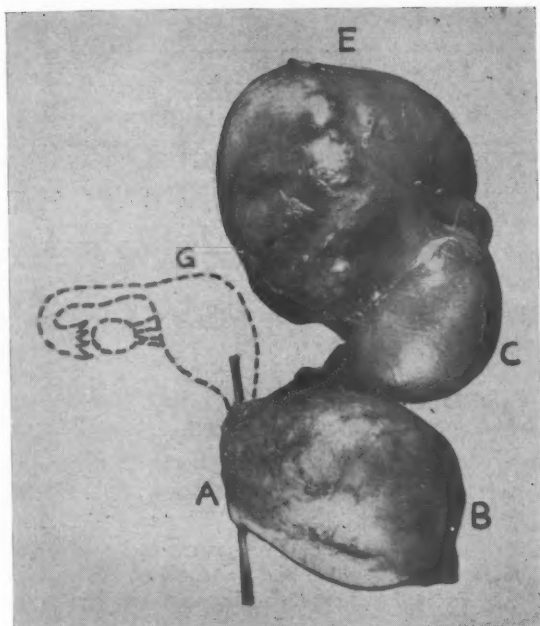


Fig. 1. Appearance of the mass in reconstructed relationship to the uterus. A, Probe in the right cervical canal. B, Large left cervix. C, Body of the left uterus. E, Large hemorrhagic cyst of the left ovary. G, Right uterus and adnexa (reconstruction).

The general physical examination was negative. The girl was well developed and well nourished. The abdomen was soft on palpation, and an indefinite mass could be felt in the lower left quadrant. The rectal examination revealed a large mass which was situated in the left pelvis and could easily be ballotted bimanually. It felt firm, elastic, smooth, and cystic, was very tender on manipulation, and apparently encroached upon the anterior wall of the ampulla of the rectum. The uterus and right adnexa could not be felt. The urine was normal. The examination of the blood showed hemoglobin 12.5 Gm. per 100 c.c., red cell count 3.95 million per cubic millimeter, white cell count 16,400 with 70 per cent polymorphonuclear leukocytes, 25 per cent lymphocytes, and 5 per cent monocytes. The temperature was normal.

The preoperative diagnosis of a left ovarian tumor was made. At laparotomy the left side of the pelvis was occupied by a dumbbell- or S-shaped firm elastic mass, smooth and bluish in color. The upper part of the mass was loosely adherent to the sigmoid colon from which it could be readily freed. The middle portion of the mass was closely applied to a small uterus

which was displaced to the right. The right tube and ovary were found in the usual relation to the right uterine cornu; they were normal in appearance. The left adnexa could not be identified. The mass was easily separated from the uterine body, but its lower pole was firmly attached to the cervix and to the vaginal vault. Attempts at separation by sharp dissection were unsuccessful. The mass could be completely removed only by amputation of most of the cervix and resection of the adjacent portion of the vaginal vault. The defect in the vault was closed by attaching the vaginal wall to the cervical stump above the line of resection, thus creating a new portio vaginalis only 0.5 cm. long.

The postoperative course was uneventful. The patient has now been followed for nearly 5 years and menstruation is normal and painless.

The mass was nodular and was removed intact, as shown in Fig. 1 in reconstructed topo-

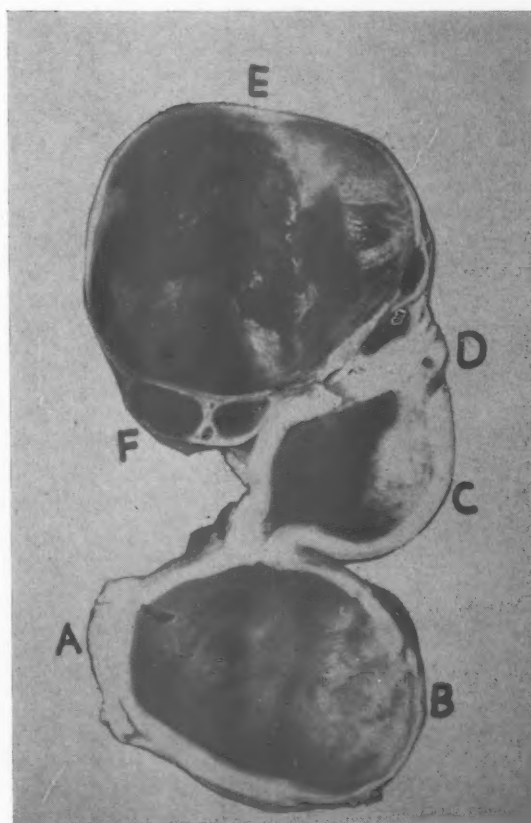


Fig. 2. Mass on cross-section. A, Flattened right cervix. B, Left hematocervix. C, Left hematometra. D, Left Fallopian tube. E, Hemorrhagic cyst of left ovary. F, Left ovary with two small cysts.

Table I

<i>Author</i>	<i>Present age</i>	<i>Age at menarche</i>	<i>Interval between menarche and dysmenorrhea</i>	<i>Chief complaints</i>
Robinson <sup>3</sup>	18	No data	No data	Severe pain in both sides of pelvis beginning with onset and lasting throughout period, growing worse at each subsequent period
Maclean <sup>4</sup>	20	12	No data	Severe dysmenorrhea, occasionally with diarrhea
Oliver <sup>5</sup>	27	19	Began with menarche	Severe abdominal pain on fifth and sixth days of period
Champel <sup>6</sup>	18	15½	Short	Painful lower abdominal colic 1 to 2 days before menstruation, subsiding toward end of 6 or 7 day period
Nemes <sup>7</sup>	26	18	8 years (partial atresia)	Severe cramplike pain in left lower abdomen starting one week before menstruation, subsiding during second half
Simon <sup>8</sup>	17	13	Short	Severe attacks of abdominal pain, more to right; occurring with period and independently; more severe recently and accompanied by vomiting and hallucinations
Grant and Rose <sup>9</sup>	17	14	2 years	Severe pain during period in right lower quadrant, radiating to back; associated with nausea and vomiting and swelling of abdomen
Maliphant <sup>10</sup>	13	13	9 months	Severe pain during menstrual period in left iliac fossa, radiating to buttock and left leg; dysuria and pain in defecation
Vernaglia <sup>11</sup>	12½	No data	No data	Abdominal pain beginning 3 days before menstrual flow; headache; decreased appetite
Embrey <sup>12</sup>	17	15	One year	Indefinite backache, little worse at beginning of each period
Guillemin <sup>13</sup>	16	14½	No pain; normal menses	Sudden discharge of chocolate-colored blood at onset and during the period at age of 16
Defendi <sup>14</sup>	18	14	5 months	Pain with onset of period, lower abdomen, more to the left
Bancroft and Baker <sup>15</sup>	20	13	Began with menarche	Persistent, dull pain with occasional sharp cramps limited to the right side, beginning first day of menstrual cycle, subsiding after 6 to 8 days
de Andrade <sup>16</sup>	13	11	2 years	Pain in lower abdomen, worse during menstruation
Randazzo <sup>17</sup>	13	No data	No data	Pain during menstruation
Willows and Wall <sup>18</sup>	12	11	2 months	Pain, cramps, nausea every 2 or 3 months with menstruation
Present case	16	12	1 year	Severe pain in left side of pelvis beginning 1 week before and lasting throughout the period; pain increasing in severity with each subsequent period

<i>Physical findings</i>	<i>Operative findings and treatment</i>
No data	Right-sided mass in the broad ligament size of an egg, containing 1½ ounces of dark fluid; identified as right uterine horn. Removal of right horn and right adnexa
No data	Left-sided mass containing chocolate-colored fluid; identified as left uterine horn. Removal of the mass
Right pelvic tumor distinct from uterus, size of small orange	Globular sac, 5 cm. in diameter, containing chocolate-colored fluid in right broad ligament. Identified as hematometra of accessory uterus and removed
Large pelvic mass, firm, elastic, tender, extending to left and up to umbilicus	Uterus bicornis with large left hematometra and hematosalpinx, atresia above internal os. Supravaginal hysterectomy
Left-sided, firm, elastic, tender tumor, isolated from uterus, reaching left pelvic wall	Uterus duplex with left-sided hematometra communicating with lower vagina through canal of 0.2 cm. in diameter. Removal of left uterus and canal
Large round mass in right pelvis attached to uterus	Incomplete uterus didelphys with right-sided hematometra. Removal of the affected horn and right adnexa
Round, smooth, firm elastic mass in lower abdomen to the right of uterus, extending to umbilicus	Bicornuate uterus with right-sided atresia and hematometra. Supracervical hysterectomy
Circumscribed spherical swelling in left half of pelvis	Bicornuate uterus with left hematometra containing ½ pint of dark blood; left hematosalpinx. Removal of atretic horn and hematosalpinx
Large tender mass in front of rectum	Two well-separated uteri; right-sided hematometra communicating with a retroperitoneal pseudocyst 10 cm. in diameter; right hematosalpinx. Removal of right uterus, adnexa and pseudocyst
Mass in right pelvis	Complete duplication of genital tract, right hematocolpometrosalpinx. Right hemihysterectomy with removal of all but lower end of right vagina
Subseptate vagina, normal cervix on left, minute orifice on right, oozing chocolate colored blood; hystero-graphy: filling of left hemiuterus, no filling on the right	Resection of the right uterus and right upper segment of the vagina
Cystic mass attached to the left side of uterus, thought to be interligamentous	Unicervical bicornuate uterus with left hematometra. Resection of left cornu, tube and polycystic ovary
Right cystic mass arising from pelvis and reaching umbilicus; hystero-graph: left cornu and cervix visualized, right cornu not visualized	Bicornuate uterus with markedly enlarged right cornu not connected with the cervix. Resection of right cornu, which was filled with old blood
Mass, size of fetal head, arising in right pelvis	Bicornuate unicervical uterus with right hematometra and hematosalpinx. Total hysterectomy
No data	Right hematosalpinx and right cystic mass continuous with uterus. At first laparotomy right salpingo-oophorectomy and appendectomy; at second laparotomy removal of cystic mass which was identified as right hematometra in a double uterus; left side, normal
Left pelvic mass, soft and boggy, considered to be an ovarian cyst	Bicornuate uterus with closed left horn, left hematometra, and hematosalpinx. Evacuation of old blood from left horn and resection of the intrauterine septum
Large, firm, elastic, smooth, and very tender mass filling the left side of pelvis; uterus and right adnexa not palpable	Incomplete uterus didelphys with large left-sided hematometra. Treatment—see text



graphic relationship to the uterus. It measured, over all, 18 by 10 by 9 cm. On section, the mass consisted of three interlocking cystic spaces (Fig. 2). The middle cyst measured 4 cm. in diameter, the lower and the upper cysts, each 7 cm. in diameter. The wall of the middle cyst had an average thickness of 1 cm.; the wall of the lower cyst was slightly thinner. Closely attached to the lateral aspect was a piece of amputated cervix (Fig. 1, *A*) which was flattened, but which contained a patent canal. It did not communicate with the cyst. The wall of the upper cyst was thin. The entire mass contained dark, chocolate-like fluid and clotted blood. The inner surface was smooth and reddish yellow in color in the lower and middle cyst and had a slightly shaggy appearance in the upper cyst. Attached to the lateral surface of the middle cyst, in the groove between it and the upper cyst, was a tubular structure measuring 5 cm. in length and 0.8 cm. in average diameter. This was identified as the left Fallopian tube (Fig. 2, *D*). A small knob of tissue on the medial aspect of the same groove was identified as the left ovary (Fig. 2, *F*). Two small cysts filled with blood-stained fluid were seen within the ovarian tissue.

Microscopic examination of sections from various parts of the lower cyst revealed epithelium with tall columnar cells, elongated nuclei, and various degrees of mucous secretory activity, characteristic of lining of the cervical canal. Sections taken from the middle cyst disclosed smooth muscle covered by a layer of endometrium—typical features of uterine wall. The upper cyst revealed numerous small protrusions, resembling flattened villi of Fallopian tube. These protrusions and the wall of the cyst were lined by a flattened cuboidal or short columnar epithelium.

#### Comment

The nature of the resected mass was suspected at the time of operation and definitely established by pathologic examination. This was a typical example of a double uterus with unilateral atresia at the level of the external cervical os. The uterine bodies were completely separated, the cervixes were partly fused, but there were two separate cervical canals. The left canal was markedly distended by retained menstrual blood (hematocervix). It communicated

with the distended uterine body (hematometra) through the internal os which, interestingly enough, had retained its usual width. The upper cyst was probably a large hemorrhagic cyst of the ovary, although the type of lining cells and the presence of villi suggested the possibility of an accessory organ arising from the Müllerian duct, such as an accessory tube.

The clinical picture was characteristic; it included all three cardinal symptoms: pelvic tumor, dysmenorrhea setting in shortly after menarche, and increasing severity of dysmenorrhea with subsequent menstruations. For comparison, 16 cases found in the literature are presented in Table I, together with the current case. The age of the patients at the time of treatment ranged from 12 to 27 years. Menarche occurred between the ages of 11¼ years and 19 years. In 2 cases dysmenorrhea occurred with the onset of menstruation; in others it followed the menarche by an interval ranging from "very short" to 2 years. In one instance, where the atresia was incomplete, the interval was 8 years; in another case, possibly also of incomplete atresia, there was no pain. All patients but the last mentioned gave a history of severe abdominal pain, which was usually localized at the site of the pelvic tumor. Pelvic mass was present in all patients (except one) whose data included physical examination, and in 13 of these the mass was localized to one side. In 4 cases, including the present, there was definite increase in the severity of dysmenorrhea at each subsequent menstrual period. This is the classical symptom of gynatresia and perhaps it would have been found more often if the nature of illness was suspected and proper inquiries made. Various concomitant symptoms such as nausea and vomiting, constipation or diarrhea, and dysuria occurred in many of the patients.

It is evident from the review of the cases that correct diagnosis was seldom thought of preoperatively and in many instances was unrecognized even during the operation. Because of this, unnecessary hysterectomies were performed in 3 cases, and in a further

3 cases repeated laparotomies were performed until the diagnosis was established and surgical correction made. Unilateral gynatresia should be considered in every instance of dysmenorrhea in a young girl when it is accompanied by a pelvic mass, and a conservative surgical approach exercised.

It is interesting to note that normal pregnancies in the other uterus may occur in the presence of unilateral hematometra (Case 15).

### Summary

A rare congenital anomaly of the female genitals—duplication of the uterus com-

bined with partial unilateral atresia—may create a well-defined clinical syndrome in young girls. This syndrome is characterized by a unilateral pelvic mass and dysmenorrhea occurring shortly after menarche and increasing progressively in severity. The correct diagnosis is of importance because conservative surgical treatment can correct the malformation while preserving reproductive function.

A case illustrating the diagnostic criteria of the syndrome and the therapeutic results is presented and the literature on the subject is reviewed.

### REFERENCES

1. Falls, F. H.: *AM. J. OBST. & GYNEC.* 15: 399, 1928.
2. Kaufmann, E.: *Pathology for Students and Practitioners*, Philadelphia, 1929, P. Blakiston's Son & Company, vol. 11, p. 1471.
3. Robinson, E. M.: *Alabama, M. J.* 23: 152, 1910.
4. Maclean, E.: *J. Obst. & Gynaec. Brit. Emp.* 20: 18, 1911.
5. Oliver, J.: *Lancet* 1: 1609, 1912.
6. Champel: *Lyon méd.* 130: 1082, 1921.
7. Nemes, A.: *Wien. klin. Wchnschr.* 34: 440, 1921.
8. Simon, H. E.: *Surg. Gynec. & Obst.* 47: 356, 1928.
9. Grant, W. H., and Rose, D.: *AM. J. OBST. & GYNEC.* 19: 555, 1930.
10. Maliphant, R. G.: *Brit. M. J.* 2: 555, 1948.
11. Vernaglia, J. B.: *New England J. Med.* 239: 732, 1948.
12. Embrey, M. P.: *Brit. M. J.* 1: 820, 1950.
13. Guillemin, A., and Guillemin, P.: *Bull. Assoc. gynéc. et obst.* 2: 594, 1950.
14. Defendi, S.: *Clin. ostet.* 53: 108, 1951.
15. Bancroft, C. E., and Baker, W. S., Jr.: *AM. J. OBST. & GYNEC.* 66: 1348, 1953.
16. de Andrade, L. C. G.: *Rev. gynec. e obst.* 1: 309, 1955.
17. Randazzo, A. P.: *J. M. Soc. New Jersey* 55: 21, 1958.
18. Willows, R. L., and Wall, M. B.: *Obst. & Gynec.* 13: 103, 1959.

# Male intersex with ambiguous external genitals and well-developed Müllerian elements

## A case report

J. T. BRADBURY, S.C.D.

R. G. BUNGE, M.D.

Iowa City, Iowa

MANY cases of male intersexuality have been reported. However, the findings in this case, namely, ambiguous genitals, well-developed uterus and Fallopian tubes, a recognizable testis on one side and a dysgenetic one on the other, are unusual.

G. K., a 7½-month-old white infant with ambiguous genitals was referred by the local physician. The pregnancy had been uncomplicated and no hormonal preparations had been administered. The child was a first-born baby delivered at term with a birth weight of 6½ pounds. The parents were told it was a hermaphrodite probably of the "male type."

Physical examination revealed a well-nourished and well-developed alert, active baby. Weight was 16⅞ pounds; height was 26½ inches, and the circumference of the head was 39 cm. The head was normocephalic and the anterior fontanelle measured 2.5 by 2.0 cm. Physical findings were within normal limits except for the genitals. The phallus measured 2.0 cm. in length and was deformed by marked chordee. An orifice was present between wrinkled "labial folds" (Fig. 1). Panendoscopy showed a separate urethral meatus and vagina at the apex of which a cervix was seen. With radiopaque material, x-ray films were interpreted as showing the presence of the vagina with a cervical shadow.

Routine laboratory results, bone age determination, excretory urograms, and excretion of

17-ketosteroids in the urine were within normal range. A buccal smear was interpreted as sex chromatin-negative.

Abdominal exploration was done, and an infantile uterus with normal-appearing oviducts was found (Fig. 2). On the left, near the fimbriated end of the oviduct, but situated more laterally than a normal ovary, was a tan oval gonad measuring 1.5 by 1.5 by 1.0 cm. Frozen section showed it to be testis. It was removed. On the right a small elongated brownish nodule of tissue was seen in the broad ligament near the fimbriated end of the oviduct and was removed. No epididymis or other Wolffian structures were found.

**Microscopic findings in the left gonad.** The architecture was that of a testis with well-



Fig. 1. The ambiguous genitals of the baby at 7 months. Endoscopic examination revealed the presence of a vagina, cervix, and separate urethral meatus.

*From the Departments of Obstetrics and Gynecology and Urology, College of Medicine, State University of Iowa.*



developed tunica albuginea, septula, and seminiferous tubules. The tubules were small, lacked lumina and tunica propia, and contained sustentacular cells and scattered spermatogonia. The interstitium was undifferentiated (Fig. 3).

**Microscopic findings in the right gonadal tissue.** This was an elongated structure with a definite tunica, somewhat wavy stroma containing germinal seminal cords at the periphery, and a central portion consisting of loose connective tissue with blood vessels. In one area the seminal cords contained germ cells. The picture was that of a dysgenetic testis (Fig. 4).

#### Comment

The adrenogenital syndrome was ruled out by the normal 17-ketosteroid excretion and the negative chromatin test. Interpretation of the x-ray films and the panendoscopic findings showed the existence of a normal vagina, urethral meatus, and cervix, which indicated the patient would probably achieve a greater degree of social and sexual satisfaction as a female (Fig. 5). Abdominal exploration was done to determine the nature of the internal genitals and to remove those least likely to contribute to femaleness. Whether feminization and menstruation would have occurred with retention of the testes is of interest; however, Wilkins<sup>1</sup> and Jones and Scott<sup>2</sup> agree that patients with ambiguous genitals or "phallic enlargement" and complete uterus, oviducts, and testes are apt to become virilized at puberty. Thus, the probability of virilization at puberty and the possibility of malignant change seem to justify the removal of the testes. Whether the clitoris will be amputated will depend on the relative size of the organ as the child grows. Estrogens will be prescribed at puberty.

This case would be classified by Jost<sup>2</sup> as representing "gonadal dysgenesis with phallic enlargement." He suggests the possibility that this condition results from a transitory impairment of testicular function (inductor action) during the time of organ-

\*In these patients with ambiguous genitals "phallic enlargement" implies a personal bias on the physician's part for femaleness; "a small penis with hypospadias" suggests a personal notion of maleness.

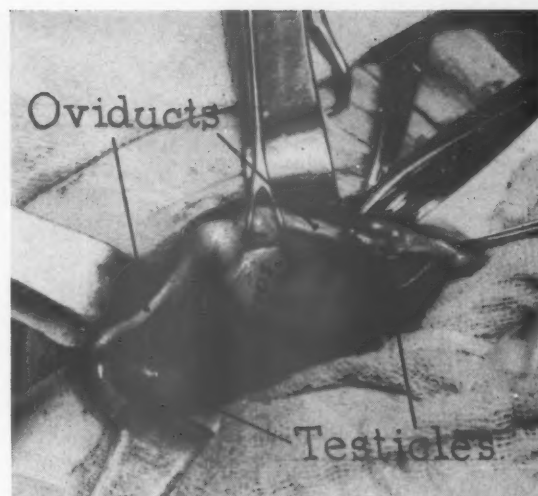


Fig. 2. Anatomical findings at the time of exploration showing uterus, bilateral oviducts, and testes. The gonads were removed.

ogenesis of the genital tract. Another possible explanation for this condition would be an asynchronism in which the time of action of the inductor influence is too early or too late to effect normal organogenesis of the genital system. In our case, then, the inductor action, if present, appeared too late to be effective (i.e., the Müllerian ducts were established and insensitive).

The ability of the differentiating gonad to exert its inductor action may not be correlated with its subsequent morphologic and functional development. The right gonad in Case 2 of Grumbach and associates<sup>3</sup> apparently exerted its inductor action too late to establish the epididymal elements but early enough to develop the vas deferens and suppress the Müllerian ducts. Photomicrographs of the testis show very few recognizable testicular elements. In our patient, neither gonad exerted effective inductor influence at the proper time, although the ultimate development of one testis exceeded that in the case of Grumbach and co-workers. Similarly, cases of anorchia represent complete regression of testicular elements initially capable of an effective inductor action which developed the epididymides and vasa deferentia.<sup>1</sup>

In the normal testis the interstitial cells

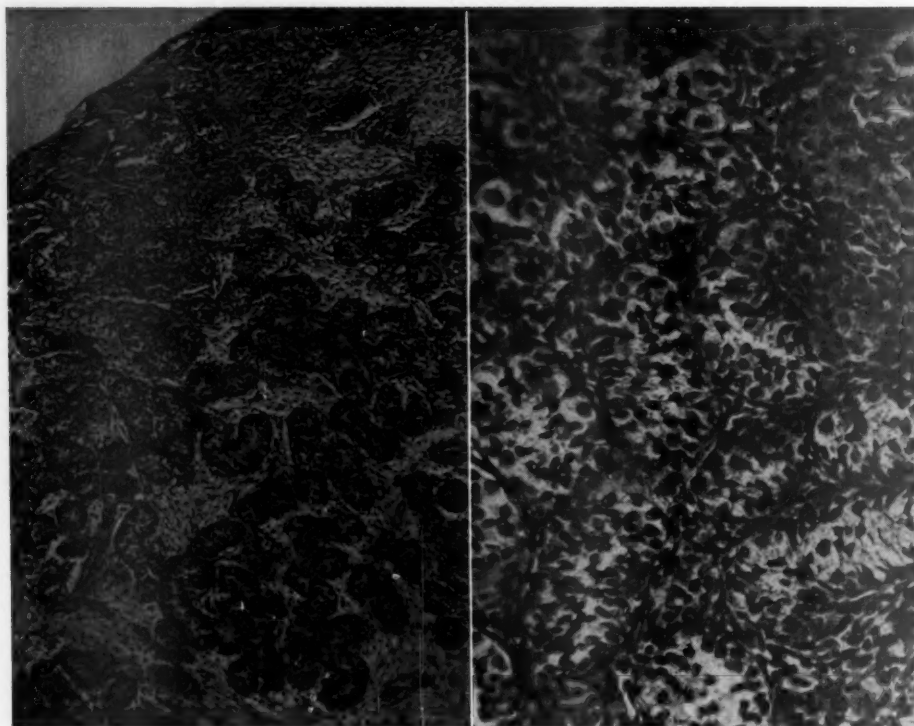


Fig. 3. Low- and high-power photomicrographs of the left testis. Tunica albuginea present with seminiferous tubules within an undifferentiated loose interstitium. There is a paucity of germinal cells within the tubules, and the majority of the cells are of the sustentacular type.

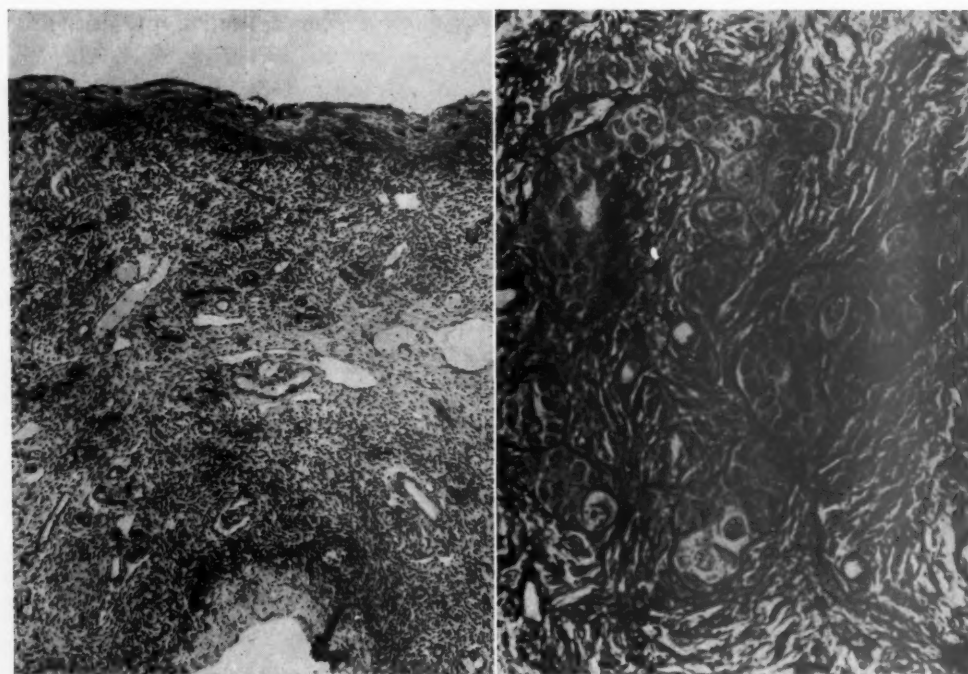


Fig. 4. Low- and high-power photomicrographs of the right gonadal tissue showing wavy stroma at the periphery with a tunica and a loose connective tissue central portion with blood vessels. The wavy stroma in some areas contains seminal cords within which two types of cells are seen, the sustentacular variety and the less numerous, larger germinal ones. Seminal cords accentuated by retouched outlines.

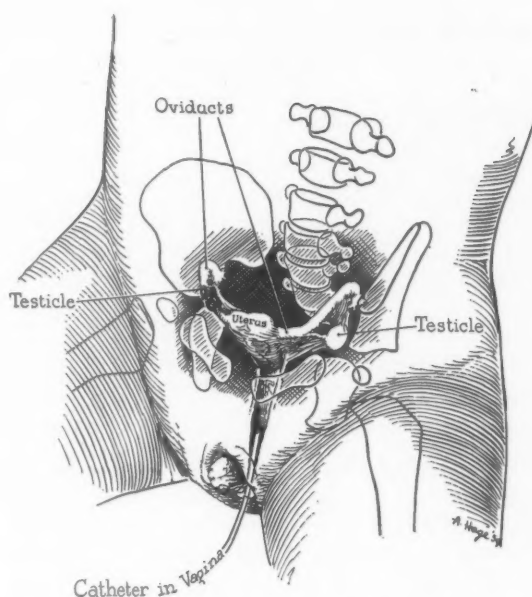


Fig. 5. Drawing combines visual, panendoscopic, x-ray, and exploratory findings.

differentiate and become hypertrophied during the latter half of pregnancy in response to chorionic gonadotrophin. It is presumed that the testes produce androgenic hormones during this late fetal period. Grumbach and

collaborators suggest the phallic enlargement may result from the functional activity of the Leydig cells of the fetal testis. We have no evidence to indicate whether or not the Leydig cells in our case may have responded in the usual way to chorionic gonadotrophin during gestation and produced "phallic enlargement." More information is needed in this area since one would experience difficulty in explaining the presence of a normally developed penis in a case of bilateral anorchia.

There has been a tendency for investigators to speak of embryonic gonadal "endocrines" or "hormones" when discussing inductor effects. It needs to be emphasized that the inductor actions are localized to the immediate vicinity of the gonads and may be unilateral or asynchronous. Until such time that an effective substance can be isolated from embryonic gonadal tissue it is necessary to discuss inductors as influences or actions and avoid terminology suggesting hormones. Any hormonal effects of fetal gonads occur late in pregnancy after the genital tract has been established.

#### REFERENCES

1. Wilkins, L.: *Endocrine Disorders in Childhood and Adolescence*, Springfield, Ill., 1957, Charles C Thomas, Publisher.
2. Jones, H. W., Jr., and Scott, W. W.: Hermaproditism, *Genital Anomalies*, Baltimore, 1958, Williams & Wilkins Co., pp. 44 and 141.
3. Grumbach, M. M., van Wyk, J. J., and Wilkins, L.: *J. Clin. Endocrinol.* 15: 1161, 1955.



# Studies on vaginal flora

## I. Frequency and significance of *Escherichia coli* isolated from the vagina

ADOLFO PÉREZ-MIRAVETE, Q.B.P.\*

HECTOR JARAMILLO, Q.B.P.

Mexico City, Mexico

SINCE the studies of Adams<sup>1</sup> on the etiology of enteritis outbreaks produced by *Escherichia coli* among children, scant attention has been paid to the bacteriologic and serologic types of the strains isolated from several parts of the human body. It has been accepted that the ability of invading bacteria to produce inflammatory lesions depends largely upon their serologic type, as has been known since the work of Bray<sup>2</sup> which showed that not all *E. coli* strains are capable of damaging host tissues. It is difficult to speak of pathogenic *E. coli* when dealing with strains isolated from vaginal discharge.

There are several tests<sup>3, 4</sup> which attempt to differentiate pathogenic from nonpathogenic strains, based on their lesion-producing ability in experimental animals. The results of these tests do not correlate, in all cases, with the pathogenicity of these bacteria in humans, but they do provide a general idea of the toxic capacity of the bacteria.

On the basis of clinical evidence, French authors<sup>5, 6</sup> broadly consider colibacillary vaginitis as a clinical entity, excluding the possibility of the fact that the microorgan-

isms represent a vaginal saprophyte. American authors accept the pathogenicity of *E. coli* in the vagina only under exceptional circumstances, associated always with incorrect perineal hygiene.

Several reports on vaginal flora agree that the isolation of *E. coli* from this site is exceptional in normal women.<sup>7-10</sup> Lash,<sup>11</sup> however, has found a 32.5 per cent incidence in normal vaginas.

The only report, to our knowledge, on a serologic study of strains isolated from the vagina is that of Neter,<sup>12</sup> who did not find any pathogenic types among 12 strains studied.

An additional reason for interest in *E. coli* in the vagina is its spermatocidal activity.<sup>13-18</sup> The possibility of transmission of maternal strains to the offspring in pregnant women is likewise worthy of mention.<sup>19, 20</sup>

In this work, toxin production by strains isolated from the vagina has been investigated. Data reported in this paper include a biochemical and serologic classification on the basis of types considered enteropathogenic. We tried to establish a relationship between the personal hygiene of the patients and the frequency of isolation of *E. coli* from vagina.

### Materials and methods

Three groups of patients attending the Gynecological and Obstetrical Departments of the Hospital Español, the Sanatorio de Hacienda, and the Centro de Salud México-

*From the Laboratory of Bacteriology, Hospital Español, the Department of Microbiology, Escuela Nacional de Ciencias Biológicas, and Sanatorio de la Secretaría de Hacienda.*

*\*Present address: Department of Bacteriology, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Mexico City 17, Mexico.*

**Table I.** Incidence of *Escherichia coli* from the vagina according to socioeconomic status of the patients studied

Hospital	No. patients studied		No. strains isolated	% with positive cultures	
	Total	With vaginitis		Of cases of vaginitis	Of total
México-España (Low)	122	101	16	15.8	13.1
Sanatorio de Hacienda (Medium)	144	126	14	11.1	9.7
Hospital Español (High)	357	317	58	18.3	16.5

España, all three in Mexico City, were studied. These institutions were selected because their patients represented the hygienic habits of three different economic levels: (1) persons from merchant and industrial families with ample economic resources; (2) government employees of a modest standard of living; (3) low-income women of limited economic resources who were given free medical attention in one of the slum sections of the city.

All samples were taken from the anterior vaginal fundus with sterile swabs. The test material was suspended in sterile saline. Each suspension thus obtained was divided into two parts: one was taken to perform direct examination for the presence of *Trichomonas vaginalis*; the other was cultivated in 5 per cent horse blood agar, G-C medium base (Difco, B289\*) with Supplement B (Difco, B276) plus hemoglobin, and Sabouraud dextrose agar (Difco, B109). Colonies formed by gram-negative bacilli were transferred to eosin-methylene blue agar (Difco, B76).

When the colonies grown on eosin-methylene blue agar showed characteristics of *E. coli*, their biochemical activities were investigated according to the method of Kauffmann.<sup>21</sup> Considered as *E. coli* were those microorganisms which formed indole, did not attack urea, did not liquefy gelatin, and gave a negative Vogues-Proskauer test and a positive methyl red test. They were then subdivided into 10 biochemical types accordingly to their fermentative activities.

\*Dehydrated culture medium produced by Difco Laboratories, Detroit, Michigan.

Sjösted's technique was used for the investigation of necrotizing toxins.<sup>3</sup> This consisted of injecting intradermally 0.1 ml. of a broth culture of *E. coli* into rabbits and observing the necrotic lesions when they appeared after 24 hours.

The production of mucinase was studied by the technique of Formal and Lowenthal,<sup>22</sup> which was used in an effort to determine pathogenicity rapidly. The test, similar to the Burnet's test for *Vibrio cholerae*, is based on the presence of enzyme activity against mucin as an index of pathogenicity.

Serologic typing was carried out with OB sera for the following enteropathogenic types: 08:K8 (L), 025:K<sub>0</sub> (L), 026:B6, 044:H12, 055:B5, 086:B7, 0111:B4, 0119:B14, 0124:B17, 0125:B15, 0126:B16, 0127:B8, and 0128:B12, with use of the Edwards and Ewing tube agglutination technique.<sup>23</sup> The purpose of the serologic typing was to identify *E. coli* with the special antigenic structure which is widely accepted as capable of producing pathologic processes on other mucous membranes.

Glycogen utilization, which we considered an important factor, was added to the Kauffmann carbohydrate tests.

#### Results and comment

Of the 122 women studied at the Centro de Salud México-España, 21 were considered normal, showing no apparent vaginal lesions, pH below 4, and a homogeneous flora formed exclusively by Döderlein bacilli; 18 of the 144 women studied at the Sanatorio de Hacienda and 40 of the 357 at the Hospital Español showed the same results.

**Table II.** Frequency of isolation of *Escherichia coli* in relation to vaginitis of different types

Type of vaginitis	Cases studied			Cases with positive cultures			Percentage		
	México-España	Sanatorio de Hacienda	Hospital Español	México-España	Sanatorio de Hacienda	Hospital Español	México-España	Sanatorio de Hacienda	Hospital Español
Normal vagina	21	18	40	0	0	0	0	0	0
Trichomoniasis	28	36	62	8	5	10	32.1	13.8	14.2
Neisserian vaginitis	0	0	5	0	0	1	0	0	20.0
Moniliasis	16	9	47	1	1	5	6.2	11.1	10.6
Nonspecific vaginitis	85	117	270	12	14	53	14.1	11.9	19.6
Vaginitis associated with <i>Str. faecalis</i>	—	—	82	—	—	39	—	—	47.5
<i>E. coli</i> in pure culture	—	—	2	—	—	—	—	—	—

**Table III.** Frequency of isolation of *Escherichia coli* in relation to the pH of the discharge

pH	Strains isolated			Percentage		
	México España	Sanatorio de Hacienda	Hospital Español	México España	Sanatorio de Hacienda	Hospital Español
3-4	0	0	0	0	0	0
4-5	0	0	3	0	0	5.1
5-6	11	12	38	68.7	86.7	65.5
6-7	5	2	17	31.3	14.3	29.4

**Table IV.** Relationship found between serotype, biochemical group, and toxin production of *Escherichia coli* strains isolated from vagina

Serotype	No. strains	Toxin production		Mucinas	Biochemical group (Kauffmann)*
		Necrotoxin	Hemolysin		
026:B6	4	4†	0	0	1 (5), 3 (3)
055:B5	4	4	2	0	1 (3), 2 (6), 1 (10)
086:B7	2	2	2	0	1 (3), 1 (7)
0111:B4	3	3	1	0	2 (5), 1 (10)
0124:B17	2	2	1	0	1 (4), 1 (10)
Nonidentified	66	57	21	2	1 (1), 1 (2), 11 (3) 1 (4), 9 (5), 3 (6) 2 (7), 20 (8), 5 (9) 13 (10)
Total	81	72 (88.8%)	27 (33.3%)	2 (2.4%)	1 (1), 1 (2), 16 (3) 2 (4), 12 (5), 5 (6) 3 (7), 3 (7), 20 (8) 5 (9), 16 (10)

\*The figures in parentheses refer to Kauffmann biochemical groups.

†These figures indicate number of positive strains.



Table I gives the percentage isolation of *E. coli* against the total number of cases studied and the number of patients with perceptible degrees of vaginitis.

The vaginitis was classified according to the predominating microorganism, as shown in Table II, indicating also the frequency of association between *E. coli* and *Streptococcus faecalis*. We considered as "nonspecific vaginitis" those cases in which the flora encountered had no well-established relationship with this condition.

Table III gives the frequency of isolation of *E. coli* from discharges of different pH values.

Table IV is a summary of the biochemical characteristics of the strains studied by Kauffmann's method, pathogenicity tests, and serologic grouping.

The data in Table I show that there seems to be no relationship between hygiene and the frequency of *E. coli* isolated from vagina, inasmuch as the group expected to have the habits of most cleanliness showed the highest percentage of isolation of these bacteria. The claims of Schwartz and Lynbrook<sup>7</sup> relating colibacillary infection of the vagina to incorrect perineal hygiene may, however, be supported by the frequent association of *E. coli* and *Str. faecalis*, which points to rectovaginal contamination (Table II).

Two cases shown in Table II are pure *E. coli* infections associated with a discharge of clearly inflammatory origin.

The apparently high degree of association between *Neisseria gonorrhoeae* and *E. coli* is rendered meaningless by the small number of cases studied.

The microorganisms most frequently associated with *E. coli* in the vagina was *Str. faecalis*; this relationship seems explicable in view of their possible common origin. Next in frequency of association with *E. coli* was *Trichomonas vaginalis*; the significance of this relationship is not clearly understood, but the old hypothesis of the fecal origin of *Tr. vaginalis* may be remembered.

Values of pH corresponding to the most frequent isolation of *E. coli* are between 5

and 6. In exceptional cases the bacteria were isolated at more acidic values, whereas isolation close to pH 7 was also frequent.

Strains of *E. coli* isolated from the vagina are not uniform in their biochemical activities, as happens with strains from other sources, mainly fecal, although the majority fell within groups 3, 8, and 10 of the Kauffmann classification.

The enteropathogenic groups clearly differentiated are five: 026:B6, 055:B5, 0111:B4, 086:B7, and 0124:B17. Of the strains studied, 15 belong to these types, representing 18.5 per cent of the total. This may give some indication of the possible pathogenicity of these strains. However, according to Sjösted, all strains which produce dermonecrotic toxins must be considered pathogenic; therefore, 86.4 per cent must be capable of producing vaginitis. When dermonecrotic zones produced by enteropathogenic type strains (from Dr. Kauffmann's collection) were experimentally compared with those produced by the injection of the strains isolated by us, the frequent observation was made that the latter produced a larger area of necrosis than did the controls.

The hemolytic test is considered less significant in view of the fact that Taylor and Charter,<sup>24</sup> Grönroos,<sup>25</sup> and Crossley<sup>26</sup> have shown that nonhemolytic strains are frequently found among pathogenic types. Hemolytic strains constitute 28.6 per cent of all the strains isolated in this work. Strains showing dermonecrotic activity but no hemolysin production were frequently found.

When the biochemical grouping is compared with the additional characteristics, it can be seen that there is no clear relationship between them. *E. coli* belonging to type 026:B6, the most common among our strains, can be found in Group 3 as well as Group 5 of the Kauffmann classification. In Group 3, necrotic strains were found with greater frequency than in other groups, but there do exist, within the same group, two strains which have no toxic activity.

The mucinase test was included in an effort to relate mucinase production with the pathogenicity of the microorganisms, but

proved useless as shown by the fact that only 2 of all strains studied produced mucinase, one of them producing no toxin and the other producing dermonecrotic toxin. Neither of the 2 could be identified as enteropathogenic types.

### Summary

1. The incidence, biochemical characteristics, and pathogenicity of *E. coli* isolated from vagina have been studied.
2. Although the incidence of *E. coli* was found to differ among the women examined, no relationship was found between personal hygiene and the frequency of isolation.
3. A great frequency of association was found between *E. coli* and *Str. faecalis* and *Tr. vaginalis*.
4. The greatest number of strains were isolated from vaginal discharges with pH values between 5 and 7.
5. All the strains studied belong to biochemical groups already well established by

Kauffmann, those of Groups 3, 8, and 10 being the most frequent.

6. Of the strains studied, 18.5 per cent were found to be enteropathogenic, the frequent type being 026:B6, and the less frequent types, 055:B5, 086:B7, 0111:B4, and 0124:B17; 86.4 per cent of the strains were found to have necrotic activity against rabbit skin, suggesting the possibility of the existence of pathogenic strains for the vagina, even though the serologic types are not well established.

7. No relationship was found between the production of hemolysin, antigenic type, and the dermonecrotic activity of the biochemical group.

8. The mucinase test in the study of pathogenic strains of *E. coli* gave no valuable data.

9. Since many of the patients from which enteropathogenic *E. coli* was isolated were pregnant, we suggest a detailed study of the transmittance of microorganism to the offspring, as a possible origin of diarrhea in newborn infants.

### REFERENCES

1. Adams, A.: Jb. Kinderh. 3: 295, 1923.
2. Bray, J.: J. Path. & Bact. 57: 239, 1945.
3. Sjösted, S.: Acta path. microbiol. scandinav. (Suppl. 63), 1946.
4. De, S. N., Bhattacharya, K., and Sarkar, J. K.: J. Path. & Bact. 71: 201, 1956.
5. Levrier, M.: Presse méd. 61: 1002, 1953.
6. Bret, J., Coupe, Cl., Bardiaux, N., and Legros, R.: Rev. Franç. gynec. et obst. 12: 837, 1958.
7. Schwartz, J., and Lynbrook, N. Y.: J. A. M. A. 147: 655, 1951.
8. Hite, E., Hesseltine, C., and Godstein, L.: Am. J. Obst. & Gynec. 53: 233, 1947.
9. Weaver, J. D., Scott, S., and Williams, O. B.: Am. J. Obst. & Gynec. 60: 880, 1950.
10. Lock, F., Dukes, M., Griffith, M., and Stout, C.: Surg. Gynec. & Obst. 87: 410, 1948.
11. Lash, J. J.: Am. J. Obst. & Gynec. 67: 138, 1954.
12. Neter, E., Webs, C. R., and Murdock, M. R.: Am. J. Pub. Health 41: 1490, 1951.
13. Rosenthal, L.: Proc. Soc. Exper. Biol. & Med. 28: 827, 1931.
14. Barton, M., and Wiener, B. P.: Brit. M. J. 2: 847, 1948.
15. Sandler, B.: Med. Press 227: 56, 1952.
16. Mathews, C. S., and Buxton, C. L.: Fertil. & Steril. 2: 45, 1951.
17. Buxton, L., Southam, A., Herrmann, W., Girvon, G., and Nadel, H.: Fertil. & Steril. 5: 493, 1954.
18. Rolle, M., and Kalich, J.: München. med. Wchnschr. 96: 579, 1954.
19. Varela, G., and Martínez, A.: Rev. Inst. salub. y enferm. trop. 13: 173, 1953.
20. Cooper, M. L.: Bact. Proc. 58: 133, 1958.
21. Kauffmann, F.: Enterobacteriaceae, Copenhagen, Denmark, 1954, Munksgaard, ed. 2.
22. Formal, B. S., and Lowenthal, J. P.: Proc. Soc. Exper. Biol. & Med. 92: 10, 1954.
23. Edwards, P. R., and Ewing, W. H.: Identification of Enterobacteriaceae, Minneapolis, 1955, Burgess Publishing Company.
24. Taylor, J., and Charter, R.: J. Path. & Bact. 64: 729, 1952.
25. Grönroos, J. A.: Ann. Med. & Exper. Biol. Tenn. 32: Suppl. 4, 1954.
26. Crossley, V., Simpson, M., and Finlayson, M.: Canad. J. Microbiol. 1: 277, 1955.

# A new pediatric gynecologic examining instrument for use in diagnosis of pediatric vaginitis

DANIEL O. HAMMOND, M.D.

*Miami, Florida*

UNTIL recently, the child with a vaginal discharge has been a relatively neglected patient. The problem is usually not a severe one, and, as a result, the common approach by the pediatrician or general practitioner has been to ignore, or perhaps to belittle, the region completely. It is the rare busy physician who even inquires as to the state of health in this system. The reasons for this lack of interest and for this state of affairs are obvious. The major one is the lack of effective examining instruments of adequate size. Another obstacle is the lack of properly sized treatment vehicles. In addition, the reluctance on the part of the physician to marshal the time and the patience needed to examine the pediatric female genital system generally results in little or no attention being paid to the problem of perineal hygiene. Moreover, the average mother is not prone to bring a child to a gynecologist directly. All of these circumstances are sad and unfortunate, for it is precisely in this area that the presence of odorous secretion can reinforce the all too common and regrettable association of the sexual perineum with fecal excretion and filth. The psychiatric implications of the situation are obvious.

In so far as adequate instruments are concerned, the presently available specula are

all rather uncomfortable for the small child, particularly where vaginitis has resulted in an irritated, painful vulva. The currently available Graves speculum as especially designed for children cannot be successfully used in a child under 8 or 10 years of age. Were an attempt made to do so, the only result would be considerable discomfort and objection on the part of the patient. The Huffman modification of this type of speculum is more useful and certainly more convenient in terms of its size and length of the speculum. However, this instrument is still not amenable for use in the smaller child. There are several types of air instruments which have been used for this purpose. The nasal and ordinary ear specula are not satisfactory since visual depth can be obtained only by opening the instruments or inserting them to their bases, which are too wide for comfort. The commonly used direct airtoscope is effective if only too large for comfort. The air speculum that is used for veterinary purposes runs into the same objection; namely, in order to be wide enough for adequate visualization, the instrument is too wide for comfort. Another general type of instrument has been used for this purpose in the form of various and sundry telescopes. The most commonly used one is the usual panendoscope that is used for investigative and manipulative activity in the urinary system. Most of these scopes that are useful for adult urologic investigation are equivalent to 24

*From the Department of Obstetrics and Gynecology, University of Miami School of Medicine, and Mt. Sinai Hospital, Miami Beach.*



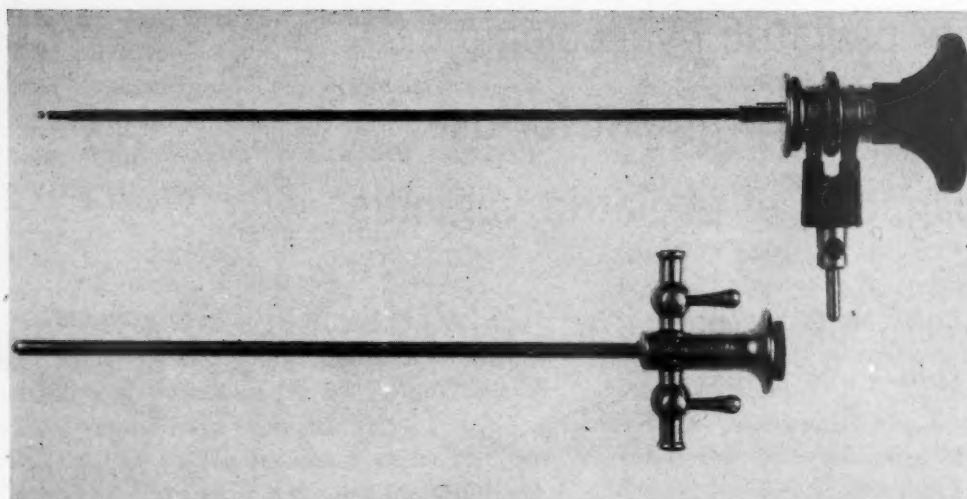


Fig. 1.

French or more and as a result are highly unsatisfactory because of their size and because of the inadequate optical systems. There is a small panendoscope that is useful for children's urologic investigation that has been applied for this purpose. This instrument is properly sized for this type of investigation but has certain optical characteristics that make it undesirable for adequate use in the small child.

A need has long been felt for a telescopic type of instrument for examination only, of proper size and optical characteristics. With this instrument, the child with vaginitis, or for that matter abnormal vaginal bleeding or congenital abnormalities, may be effectively examined on an outpatient basis with authority. When this is done, treatment can be scientific, not haphazard, and foreign bodies and tumors can be quickly discarded as parts of a differential diagnosis, without hospitalization and utilization of an operating room.

A realization of the traumatic effects of hospitalization on children and the subsequent psychological deterioration has become a matter of general interest in more than one discipline. Both psychiatric and pediatric specialists are very much aware of the fact that a child removed from his source of security and affection and placed in a hospital with strange surroundings, with strange people, and strange instruments very

quickly becomes a matter of proper psychological concern. This does not take more than 12 to 24 hours to develop and will reach a rather serious state within a short time of 2 days. Recently an editorial in the *Journal of the American Medical Association* stated, "For a child to be separated from [his] parents, placed in strange surroundings, and subjected to a variety of unpleasant proceedings is apt to be psychologically traumatic under the best circumstances. . . . If an anesthetic must be given, the child may fear that he will be or has been mutilated while asleep. . . . Anything that can be done to prevent or minimize psychic trauma attendant on hospitalization of children is sure to be worth the effort. Some admissions could be avoided through a greater use of out-patient service."

In the gynecologic area greater effectiveness of an outpatient service would be afforded by availability of an instrument that is small, effective, available with a minimum amount of new equipment, and useful for interpretation by anyone who is unskilled in endoscopic examination. A new instrument is therefore offered here, partly because of its increased effectiveness and greater usefulness to the physician and partly because of the awareness that the use of such an instrument will make gynecologic investigation less of an ordeal and more commonplace for the small child.

### Description of instrument

The new instrument offered is a modification of the McCarthy pediatric panendoscope. The modification is in the optical characteristics of the objective lens. In this instrument, unlike the pediatric cystoscope, the objective lens is placed in such a way that it is a forward-looking rather than an oblique-looking lens. In addition, the lens is so modified as to permit visualization of material that is in contact with the lens or at a minimum of 1 mm. from the lens. In this manner, examination of a lumen that is very small and that is painful if moved becomes a very easy process. By this means, most of the examination that is necessary on the small child need not be relegated to the hospital unless the child is so emotionally disturbed by the time she gets to the gynecologist's office that gentle manipulation and investigation from below are not feasible even with very tiny instruments. This would then be an emotional justification for hospitalization but not a physical one.

Thus, the new instrument is essentially a modification of an old instrument (Figs. 1 and 2). The McCarthy pediatric panendo-

scope has been modified by removing the catheter horn that was a midline element of the previous instrument. It has also been optically modified so that the scope is a forward-looking scope which focuses directly on or at the level of the objective lens. This is, therefore, a small instrument approximately 10 to 12 French in diameter which is available for carrying out vaginal examinations on very tiny children without displacing to a major extent the surrounding structures of the vagina. In contrast to the parent instrument, with this instrument the lumen of the vagina does not require distention in order to provide optical working space. As a result, distention of the vagina with air or water is not necessary. However, irrigation facilities have been included in this instrument because of a necessity of washing away vaginal secretions or blood or both from the objective lens. Without this element, visualization will be quickly impaired by the vaginal secretions. The instrument has not provided for any manipulative procedures, because fewer than 5 per cent of the patients examined show foreign bodies which need attention or tumors which need biopsy. Un-

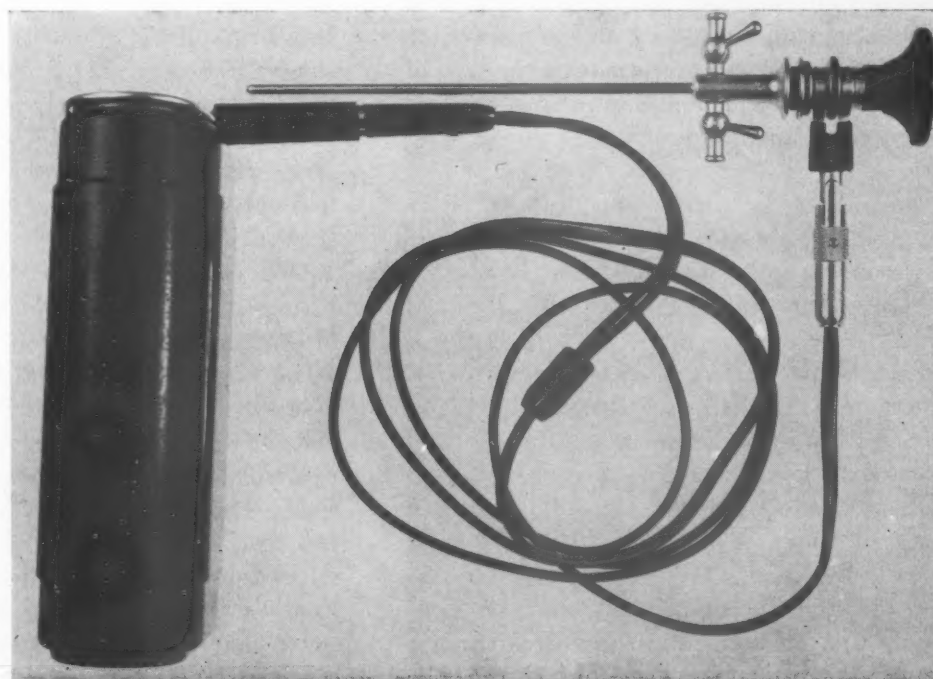


Fig. 2.



Fig. 3.

der these circumstances, it was felt that the inclusion of manipulative facilities would increase the diameter of the instrument sufficiently to defeat the purpose of the small design.

In the use of the instrument, only a few additional materials are needed. In most circumstances, a sufficient and proper source of illumination can very easily be the type of transformer that is found in most offices and is more commonly used for illumination in sigmoidoscopy and other diagnostic procedures. The light source on this type of instrument is somewhat more potent than the bulb in the instrument described here. As a result, resistances are necessary in the circuit; these may be easily obtained from a medical supply source. In view of the concern that most individuals have about examining patients with instruments that are directly connected to a 110 volt wall power source, it has been advised by most authorities that a battery source of power is much safer and should be used in any endoscopic instruments. By doing so, one can avoid the possibility that an accidental short circuit might injure the patient by virtue of a direct volt-

age being applied to an anatomical structure. Therefore, the battery type source which is ordinarily used for cystoscopy is to be preferred. Another implement which is required for use of this instrument is a source of water. It has been my practice simply to attach a commonly available intravenous tubing to one of the apertures on the shaft of the sheath and attach to it a small bottle containing water. Any small receptacle can be used for this purpose. One need only have clean apparatus. It is not necessary to use sterile equipment under these circumstances.

One of the problems that arises in any investigation of small children is the problem of approaching them for the purpose of doing such an examination. All too frequently, the patients that come to the gynecologist's office have been instrumented and manipulated by one or more previous physicians. The large majority of the time this has been done with relatively few adequate safeguards for comfort of the patient. Because of this and because of the usual reticence that most children experience in the physician's office, the child is "gun shy" as



far as having the perineum examined is concerned. If this is the case, and it can be easily ascertained that such is so during the initial episode of taking a history, it is very easy to give the child either some oral liquid sedative or a rectal suppository containing some material such as chloral hydrate. In view of the fact that barbiturates frequently excite small children, chloral hydrate has been selected as a sedative of choice. It is apparent that in view of the size of the instrument, pain is not going to be a major problem associated with a vaginal examination. Therefore, anxiety only is the obstructive attitude which may be met on the part of a small child. If these sedatives are given by mouth or by rectum, one can generally wait for approximately 20 minutes for their effect and then have a subject who is at least not fearful and anxious and who will generally submit to examination with relatively small amounts of anxiety. It might be worth while here to note that the presence of the mother in the examining room or of a close relative gives the child an individual who is familiar and who is a source of emotional support (Fig. 3). Under these circumstances, most children will submit to examinations that they would not allow were the parent or other relative not in the room. This is not always the case; whether or not to exclude the anxious parent is always a problem.

#### Description of technique of examination

In view of the fact that this is a matter which has not been too commonly discussed in the literature, it was felt that a short description of office technique might be worth while in this discussion. When the child is brought into the consultation room for an initial history taking, she is observed for anxiety or tension. A fearful mien or evidence of such anxiety on the part of the mother or child is justification for sedation. This matter is discussed quickly with the mother and the sedation is then given to the child if necessary and if indicated. History taking is subsequently finished. The child is referred to the bathroom for the purpose of emptying the bladder and securing a urine

specimen for examination. The child is then placed on the examining table and a few moments are spent acquainting the child with the instruments that are to be used (Fig. 4) and with the purpose of the examination in general. The child is then placed in stirrups if she is large enough. If not, the mother is instructed as to the technique of holding the feet apart from above, a common pediatric occurrence. The child is then examined externally with the usual technique of spreading the labia and drawing them downward toward the back. In this manner, the labia are opened sufficiently to visualize the clitoris, and some information can be obtained as to the state of the hymen and the vagina. Examination is directed to the rectum in order to determine the presence or absence of excoriation in this area, which would suggest the presence of pinworms. A pinworm slide is generally taken from the vaginal orifice. A gentle rectal examination with the small finger is then utilized as a part of a bimanual examination of the pelvic organs and the lower genitourinary tract. The gastrointestinal tract is evaluated also at this time. In the event that the vaginal discharge is the presenting symptom, cultures are taken. These cultures are taken in a manner so as to preclude contamination from the vulva and from the introitus itself.

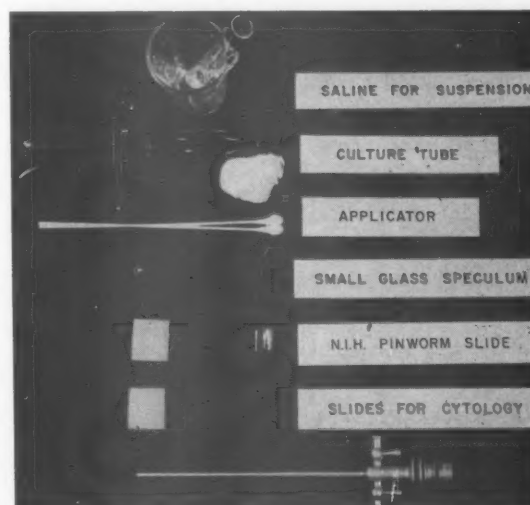


Fig. 4.

Several techniques are available for this purpose. It has been my practice to utilize very simple instruments for the purpose of accomplishing this goal. A small length of 5 mm. glass tubing which has been broken to a length of approximately two inches is used. The ends of the glass tubing have been fired so as not to injure the child during insertion of the tubing into the vagina. Applicators are used for obtaining cultures which are customarily used in this hospital for nasopharyngeal swabs. These are long lengths of steel wire which are quite pliable, to the end of which has been applied a small piece of cotton. The cotton is secured by collodion. This applicator is then put into a large tube that is very much like a urea nitrogen tube. Along with the applicator in the large tube is placed a smaller tube with broth. The cotton applicator is of such a size that it can be easily placed inside the large tube and also inside the small tube where the broth will keep it wet until such a time as it can be taken to the laboratory and plated. The applicator is kept sterile by means of a cotton plug in the large tube. After cultures have been obtained, one of these applicators is used for the purpose of obtaining a cytology smear from the vagina and also a hanging drop or saline suspension preparation for diagnosis of trichomonas or for doing a bacterial spread from the vagina if desired. The glass tubing is then withdrawn and discarded since it is very inexpensive and can be cleaned only with difficulty. The instrument described here is then inserted into the vagina; the yoke attachment for power is attached and the small tubing from the water source is attached to the side of the shaft. No lubrication need be used for this purpose since the instrument is small enough so that it can be inserted past even the most irritated vulvar area without discomfort to the child. The instrument need not depress the rectal vaginal septum in order to get sufficient optical viewing space since the previously described optical characteristics make it possible to examine the vagina and its contents without distorting or disturbing the local geographic structures to any extent.

In the event that any foreign body is found or in the event that a tumor is found that requires biopsy, the instrument is removed and an air scope is used for this purpose. If this is not possible in the office, the child is referred to the hospital for this type of examination under anesthesia. That this occurs very rarely is a factor to be noted in the usefulness of the instrument.

#### Techniques of treatment

In view of the fact that the vaginitis that is commonly found in the child is identical to the type of vaginitis found in the menopausal individual, the same principles of treatment generally hold. It is a matter of common knowledge that the epithelium in the vagina of the premenarchal child is very thin and essentially resembles an atrophic type of epithelium. It is low, and cytologic smears taken from it reveal many basal-type cells. It is very susceptible to bacterial invasion. This is particularly true if the patient has indulged in self-manipulation. Under these circumstances, most frequently the diagnosis is a nonspecific bacterial atrophic vaginitis. It is rare that a specific bacteria is involved. However, in these circumstances, the *Escherichia coli* bacterium is the usual offender. Rarely, streptococci or staphylococci are found. Occasionally, pseudomonas is the major organism. Also, it is rather rare to find the gonococcus involved in a specific infection. Tuberculosis is very rare. Mycotic infections are fairly common, particularly in view of the propensity of the average general practitioner or the pediatrician to give a "shot of penicillin" for a cold. This commonly results in an overgrowth of monilia in the vagina, and the child as a result has iatrogenic monilial vaginal infection. Pinworm infestation is frequently found, although there is disagreement as to whether the worms in the vagina grow there or are transplanted from the rectum by the fingers of the patient.

Treatment should be directed toward the eradication of the basic pathology. In the case of the nonspecific bacterial infections, the treatment is essentially that of supplying

an antibacterial agent in proper form. The most commonly used preparation has been the nitrofurazone (Furacin) suppository type of treatment employing the urethral-type suppositories. In the event that the atrophic aspect of the epithelium is impressive, the Furestrol urethral suppositories may be used instead. These small urethral suppositories are approximately 2 to 3 mm. in diameter and can be easily inserted in the infantile vagina. In the event that other preparations are indicated, small applicators that are generally used for introduction of ointments into the rectum may be adapted to this purpose. In addition, plastic tips that are available on the market as plastic eyedroppers can be used as adaptors to make introduction into the vagina an easy technique. Some commercial companies supply adaptors that are available for their commercial products that can be used for children. Douching is usually not necessary but is effective in removing the mucopurulent secretions and allowing the therapeutic agent to effect more quickly an improvement of the situation. In the younger children, direction as to self insertions is usually not possible. As a result, the mother is instructed as to the insertion of this medication while the child is still on the examining table. In older children, it is possible to have them insert this medication themselves. It is desirable to limit the duration of the medication as much as possible, since manipulation in this area always raises the question of psychological damage associated with the therapy itself.

Instruction in techniques of personal hy-

giene remain an integral part of therapy. Proper washing and postexcretion cleansing remain part and parcel of treatment. The use of an antibacterial soap has also been found valuable. Some effort to alleviate local discomfort with the usual medications (corn starch, oatmeal, cortisone, etc.) is usually necessary in the acute phase of the inflammatory reaction. Occasionally, the persistent use of acid soaps is contraindicated.

### Summary

In summary, this presentation has as its purpose the introduction of a new type of diagnostic instrument for performing vaginal examinations on very small children. The instrument is a small telescope that has been optically modified so as to focus immediately on the objective lens. The irrigation facilities have been supplied for the purpose of keeping the objective lens clean of mucopurulent material or blood if it is present. Some notes as to techniques for pediatric examination and treatment have been included.

Note: This instrument was displayed for the first time at the American College of Obstetrics and Gynecology at Atlantic City in April, 1958. The instrument will be produced by American Cystoscope Makers, Inc. Furestrol suppositories were supplied by the Eaton Company.

---

### REFERENCE

1. Editorial, J. A. M. A. 168: 1376, 1958.

350 N.E. 15th St.  
Miami 32, Florida



## OBSTETRICS

### Na<sup>24</sup> uterine muscle clearance in late pregnancy

ROBERT LANDESMAN, M.D.

ROBERT CHARLES KNAPP, M.D.

*New York, New York*

UTERINE function may be investigated by the use of Na<sup>24</sup> injected into the myometrium. The evaluation of this test could then provide information which would have clinical significance. Recent reports in the literature suggest that this clearance may be useful in the management of some abnormalities in late pregnancy.

Kety<sup>9</sup> in 1949 proposed that, if an isotope of one of the common cations, such as sodium, be deposited in the tissues, its rate of clearance from the tissues, when plotted semilogarithmically, would yield a straight line. The slope would reflect the clearance rate and would serve as a measure of the ability of the local circulation to remove the substance from the point of deposition. Browne and Veall<sup>2</sup> injected doses of 10  $\mu$ c of Na<sup>24</sup> in 1 c.c. of normal saline into the

choriodecidual space of 10 patients at term and found the half-life clearance time was 21 seconds in normal pregnancy and 65 seconds in toxemia. (The half-life clearance time is the time required for the radioactive counting rate as measured at the local injection point to fall to half its initial value. It is clearly distinct from the half-life of the material injected, which is a measure of the decay of the radioactive substance itself, and not the local removal rate.) The authors indicated that this was a direct measure of relative blood flow in the placental pool. Because of the difficulty in reaching the placental bed, Morris, Osborn, and Wright<sup>11</sup> injected the Na<sup>24</sup> into the uterine wall directly below the umbilicus in 38 cases. A considerable difference was demonstrated in time to half-life clearance; in the normal patient it was 4 minutes; in those with mild pre-eclampsia, 7 minutes; and in those with severe pre-eclampsia, 15 minutes. The same authors, along with Hart,<sup>12</sup> showed that the uterine muscle clearance during exercise has an increased half-time, and following exercise after rest there is a tendency for the clearance to return closer to normal. Johnson

*From the Department of Obstetrics and Gynecology, New York Hospital-Cornell University Medical College.*

*This investigation was supported by a grant from the United States Department of Health, Education and Welfare, National Heart Institute, H1100 (C-6, C-7).*

*Presented at a meeting of the New York Obstetrical Society, Jan. 12, 1960.*

and Clayton<sup>8</sup> reconfirmed the above work using somewhat larger doses, 20  $\mu$ c of the sodium. Moore and Myerscough<sup>10</sup> studied 87 cases and indicated that there was a significant slowing of clearance rate in the normal primigravida past term and in patients with pre-eclampsia.

In this country, Taylor and associates,<sup>14</sup> using Na<sup>22</sup> with a half-life of 2.6 years, with 5  $\mu$ c in 0.2 c.c. of saline, studied the uterine muscle clearance in 127 patients. As the British authors had found, the half-life of clearance in patients with more severe toxemia was elevated over that of normal subjects. Wright and associates,<sup>15</sup> in 48 patients during the course of labor found that the half-life time was over 12 minutes in both fetal distress and prolonged labor. The average normal patient during labor showed normal clearance.

Johnson and Clayton<sup>7</sup> injected 50  $\mu$ c of sodium intravenously and determined the uptake directly over the uterus. They found subnormal uptakes in patients with advanced toxemia.

#### Method

The basic equipment includes a scaler (TMC), an automatic counter (Simplex), and a two-inch sodium iodide crystal (Nuclear-Chicago) surrounded by a half-inch lead column mounted on a mobile carrier which can be accurately adjusted over the patient's abdomen. Na<sup>24</sup>, as Na<sup>24</sup>CO<sub>3</sub>, with a half-life of 15.1 hours, is received by shipment weekly from Brookhaven Laboratories. This white powder is dissolved in normal saline, the pH is adjusted to 7.4, and the solution is sterilized. The activity is determined by comparing its counts per minute with those of a source of known activity. For our use, the Na<sup>24</sup>Cl is diluted so that the activity equals 1.6  $\mu$ c per cubic centimeter. An initial background count is taken. The patient is placed supine or on the side with bladder empty, and the abdomen is prepared surgically. A weal of 1 per cent Xylocaine is placed 2 cm. below the umbilicus and either 2 cm. to the right or to the left of the midline. A 23 gauge needle

is passed through the abdominal wall, through the peritoneum, and into the uterine muscle. The patient would generally move slightly and indicate some slight pain as the needle passed the peritoneum. If the needle is in the uterine wall, a deep inspiration will produce a deflection of the needle upward and expiration will produce a deflection of the needle downward. A very deep regular respiratory movement may dislodge the needle from the uterine wall. The stylet is then removed and a 5 c.c. syringe containing 0.8  $\mu$ c of Na<sup>24</sup> in 0.5 c.c. of saline is injected into the uterine wall. Aspiration is first performed, and if blood or fluid is obtained, the needle is withdrawn and another area is entered. Immediately following injection of the radioactive material, the stand is mounted directly over the injection spot and the crystal is placed firmly against the abdomen at the point of injection. Blood pressure readings are made routinely prior to and at the termination of the test. The clearance is usually complete in from 8 to 12 minutes, and the counting is continued usually for a total period of 20 minutes. Check point counts are made over the opposite side of the abdomen, over the right femoral vessels, and at a third area directly over the heart. If the clearance is rapid, the heart level is usually about the same as the final count over the point of injection. If the clearance is slow, the heart count is less and will approximate that of the two other check points. Ideal initial counting rate following injection runs between 10,000 and 40,000 counts per minute. The sodium ion is generally injected 5 cm. away from the crystal, 2.5 cm. of which distance is through the abdominal wall. Another 2.5 cm. is measured from the end of the cone to the fore-point of the crystal. This distance varies somewhat, usually about 1 cm., depending upon the thickness of the abdominal wall.

The counts per minute are plotted as a function of elapsed time on semilogarithmic paper. In a typical normal curve, the counting rate drops rapidly at first and, after 15 or 20 minutes, has flattened out.

The counting rate in the flat region is the equilibrium background rate. We note that in this period the  $\text{Na}^{24}$  (with a half-life of 15.1 hours) has itself decayed a negligible amount. The resultant curve is analyzed into exponential components such that the sum of the components equals the original (resultant) curve. The analysis into components is accomplished by first subtracting the equilibrium background rate from the points on the original curve. When plotted on semilogarithmic paper, the differences lie along a straight line, except for a few points at low values of elapsed time. The differences (remaining residuals) between these few points and the straight line are then themselves plotted, and a second straight line fitted. If any residuals with respect to the second straight line remain, a third straight line is plotted. This is rare, since usually only one or two exponential components (and the equilibrium rate) are present.

Each of the straight lines (components) on the semilogarithmic paper represents an equation of the form:

$$m = m_0 e^{-\frac{\log_e 2}{T} t}$$

where  $t$  = time measured from the time of injection;  $m$  = counting rate at time  $t$ ;  $m_0$  = initial counting rate (at time  $t = 0$ );  $T$  = half-life clearance time, i.e., the time required for the counting rate  $m$  to fall to a value of  $m_0/2$ , half the initial counting rate; and  $e$  = base of natural logarithms.

The half-life  $T$  for each component is obtained. When more than one half-life is present, the initial shortest period is taken to be the characteristic one. Fig. 1 demonstrates a normal clearance curve and the two straight line components derived by this method. The first half-life of 0.5 minutes represents the maximum clearance rate and is used for comparison. In other cases, more typical of abnormal conditions, the initial counting rate remains constant for several minutes and then falls at a relatively slow rate which can be analyzed into an exponential component. In some cases the

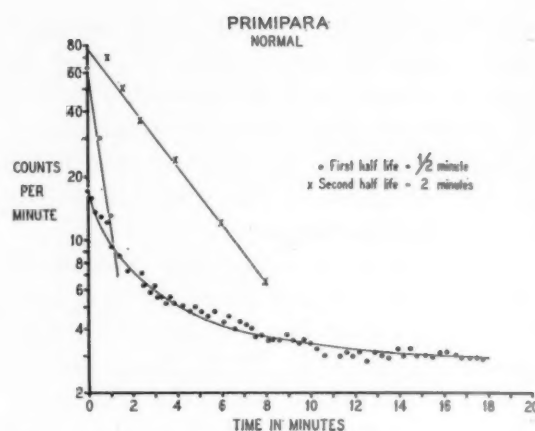


Fig. 1. A normal clearance curve and the two exponential components,  $x$  and  $o$ . The faster of the two, or  $o$ , is most characteristic and is used as the half-life for the clearance.

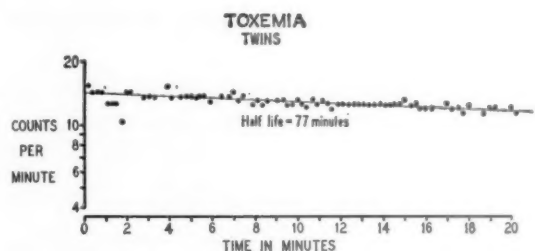


Fig. 2. The lack of clearance associated with twins, hypertension, and fetal distress.

equilibrium background rate is never reached, and an estimate of time for decay to half the initial counting rate is made.

In this study, 126  $\text{Na}^{24}$  uterine muscle clearances were performed on 114 patients. A bloody tap resulted on rare occasions. Occasionally, early in the course of this series, the labeled saline was placed in the amniotic fluid. Nine clearances were discarded owing to improper injection or technical difficulties with the scaler. Because of the known effects of irradiation on living tissues, it is important to calculate the total irradiation dosage which was given to the maternal gonads during the  $\text{Na}^{24}$  clearance. We are presently using  $0.8 \mu\text{C}$  of  $\text{Na}^{24}$ , as indicated in Table I. This is equivalent to 1.1 milliroentgens. The radiation dosage is calculated on the known half-life of the  $\text{Na}^{24}$ , which is 15.1 hours, and also on the



rate of excretion of the sodium ion from the blood stream. The radiation dosage is calculated for a prolonged clearance which would produce the maximum dose in the uterine muscle. It is seen from Table I that the total dosage received by the maternal gonads from this procedure is about 200 times less than that received from the usual flat plate of the abdomen, 600 times less than that of an intravenous pyelogram, and 3,000 times less than the usual hystero-gram series. At present, the maximum permissible dose for Na<sup>24</sup> is 5  $\mu$ c or 100 millirads per week continuously over a period of a year.

### Results

**Normal group.** Among a total of 57 patients with so-called normal pregnancies, 60 clearances were performed. On the basis of careful analysis of the data, it appears that the normal half-life clearances are less than 6 minutes. The half-life clearances of 6 minutes or over would appear to be in the abnormal group. (See "Comment" for elaboration on the choice of 6 minutes.) Table II shows the total number of normal and abnormal clearances in each group of patients using the above limit for normal.

Among the 10 patients with abnormal clearances in the normal group, there were 5 that had no other associated factors which might explain the altered clearance. All 5 others had variations from the normal which could possibly explain the prolonged clearance: 2 patients had fetal distress when in labor; one infant was very small (2,470 grams) for the duration of pregnancy (40 weeks); another infant was excessive in size (4,820 grams); and one patient showed mild supine hypotension and complained of dizziness during the clearance study. Without correcting for possible abnormalities which are listed above, 18 per cent of patients in the normal group had prolonged clearances.

### Toxemia.

**Chronic hypertension.** Of the 23 patients with chronic hypertension, 10, or 43 per cent of the group, had abnormal clearances. Of the 10 abnormal curves, 9 showed

a small period before the drop which was completely flat. In the group of 13 with normal clearances, there were 3 patients who had short one- or two-minute periods of no clearance before the normal drop. In the chronic hypertensive group as a whole there were 12 patients who had this flat clearance phenomenon at the beginning of the test. A patient with twins and known chronic hypertension had an extremely prolonged clearance as shown in Fig. 2. The clinical course is detailed below.

**Patient H. A.** (New York Hospital No. 730158; Clearance No. 33). This 23-year-old gravida ii, para i, with one living child, was admitted in the thirty-fifth week of pregnancy with a blood pressure reading of 140/100. On the day of admission, the sodium clearance was very flat. The following day the patient went into spontaneous labor with twins. The uterus was extremely tense and the fetal heart of the Twin B was grossly irregular and 80 per minute, indicating fetal distress. A low flap cesarean section was performed. The first twin weighed 1,810 grams; the second twin, weighing 1,720 grams, was living but in very poor condition and died 48 hours post partum. At the time of operation there was extreme blanching of the anterior wall of the uterus. No hydramnios or placental separation was evident.

Table I. Radiation dosage to maternal gonads

Procedure	Millirads
0.8 $\mu$ c Na <sup>24</sup> Cl in uterus	1
Flat plate of abdomen	200
Intravenous pyelogram	600
Pelvic series (3 films)	1,000
Hystero-gram	3,000

Table II. Normal and abnormal clearances

Group	No. of patients	Normal clearance (%)	Abnormal clearance (%)
Normal	57	82	18
Toxemia	40	55	45
Mild	34	62	38
Severe	6	17	83
Labor	13	85	15
Fetal distress	9	33	67

**Pre-eclampsia.** Of a total of 13 patients with pre-eclampsia, there were 6 abnormal half-life clearances and these were all flat lines. Of the 6, or 46 per cent of the group with abnormal curves, one was associated with very severe toxemia. There was no fetal loss. In one patient, clearances were done on three occasions. The results are shown in Fig. 3. There was a progressive change in the clearance over a period of 2 weeks, the half-life becoming longer as the patient came close to term. The clinical course is detailed below.

**Patient L. H.** (New York Hospital No. 802836; Clearance Nos. 52, 57, 59). The patient was a 36-year-old gravida iii, para ii, with 2 living children, who developed evidence of hypertension in the thirty-eighth week of pregnancy and was delivered in the fortieth week by cesarean section. The infant weighed 4,840 grams. In the thirty-seventh week a clearance was performed which showed a normal half-life time. One week later, when the hypertension had become more severe, the clearance demonstrated an increased half-life, but within nor-

mal limits. Finally, a third clearance during the week of delivery showed a distinctly abnormal flat line.

**Hypertension with superimposition.** There were 7 clearances performed on patients with hypertension and superimposition of acute toxemia. There were a total of 4 patients. Three had 2 clearances; there was obvious good reproducibility of the clearance curve on each occasion. There were 2 abnormal clearances with a half-life of one of 16 minutes and the other of 8 minutes.

**Fetal distress.** Nine patients had definite evidence of fetal distress during labor, characterized by the passage of large amounts of meconium and reduction of the fetal heart rate to a level below 90 per minute. Eleven clearances in all were carried out on this group, and on one patient 3 clearances were performed at weekly intervals. In 8 of the patients exhibiting fetal distress, the clearances showed a characteristic flat component which lasted 2 minutes or more. In the total group there were 6 abnormal half-

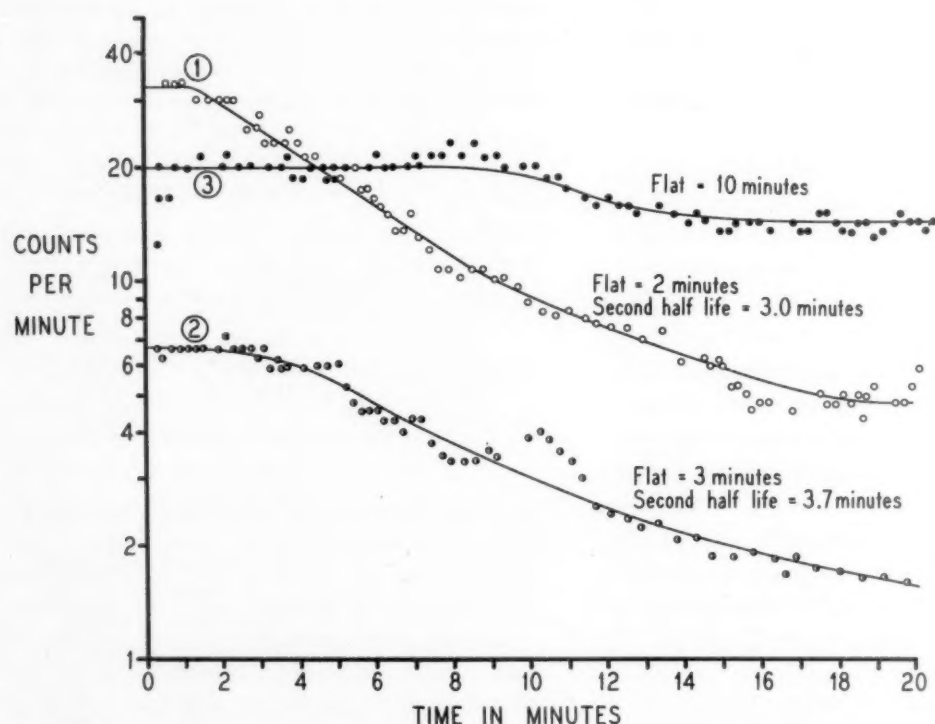


Fig. 3. Three clearances on the same patient at weekly intervals beginning at the thirty-seventh week, showing progressive prolongation of clearance half-time and flat initial periods. The toxemia became more severe over this period.

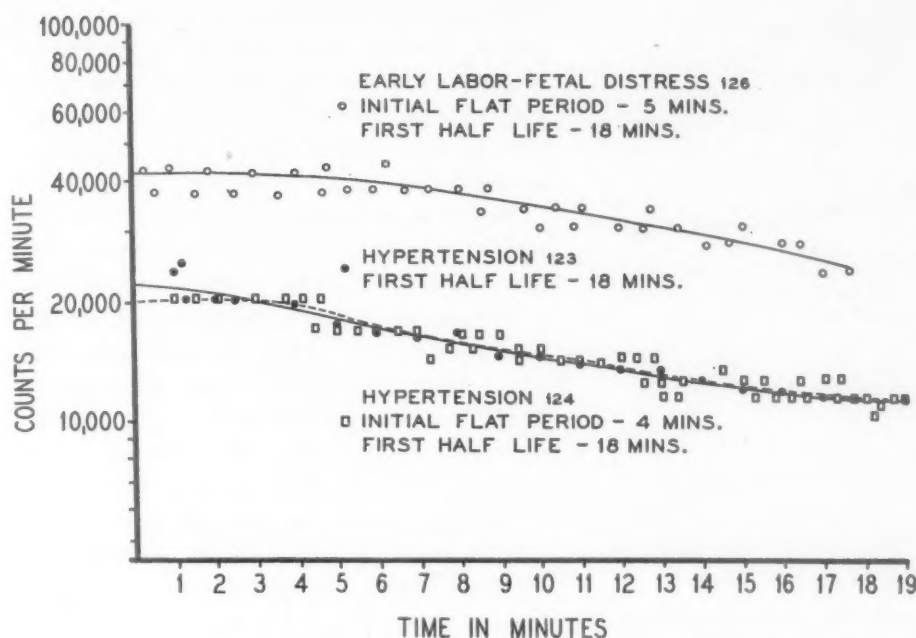


Fig. 4. Three abnormal clearance patterns in a hypertensive patient over a period of 3 weeks showed good reproducibility of the clearance studies.

life clearance times, or an abnormal rate of 67 per cent. One infant in this group—a second twin which exhibited fetal distress during labor—died. The clinical course of the patient with 3 clearances is detailed below. The 3 curves obtained are shown in Fig. 4.

**Patient S. H.** (New York Hospital No. 825949; Clearance Nos. 123, 124, 126). The patient was a 30-year-old gravida iv, para i, with no living children. In 1957 an infant 2 months premature was delivered and died. The patient developed elevated blood pressure of 140/110 in the thirty-fourth week. She was maintained on diuretics and careful weight regulations with weekly observation. At the time of the onset of labor in the fortieth week, the blood pressure rose to 168/116, and there was 1-plus edema without proteinuria. Early in labor there was an episode of fetal distress with the heart rate falling to 90. Following rupture of the membranes, large amounts of meconium escaped from the uterus. Because of a sudden drop in the fetal heart to 80 after full dilation, a low midforceps delivery and repair was required. The infant, weighing 2,410 grams, was grossly normal and was stained with meconium. All 3 clearances obtained (thirty-eighth, thirty-ninth, and fortieth

weeks) were abnormal, and the half-life times obtained were essentially the same (18 minutes).

Four of our patients had an Apgar<sup>1</sup> score of 5 or less. Three in this group had abnormal clearances. One was stillborn, and a second died in the neonatal period.

**Labor.** Thirteen clearances were performed during labor. The clearances were equally divided between nulliparous and multiparous patients. The dilation of the cervix varied from 1 to 5 cm. during the test. In general, the pattern of clearance was normal during labor except for two

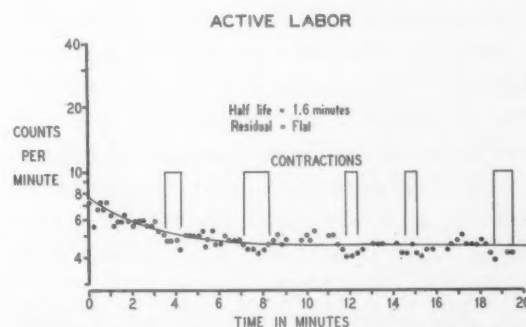


Fig. 5. Normal clearance curve and half-life associated with labor. The V dips in the curve appear to correspond to the time of the contractions.



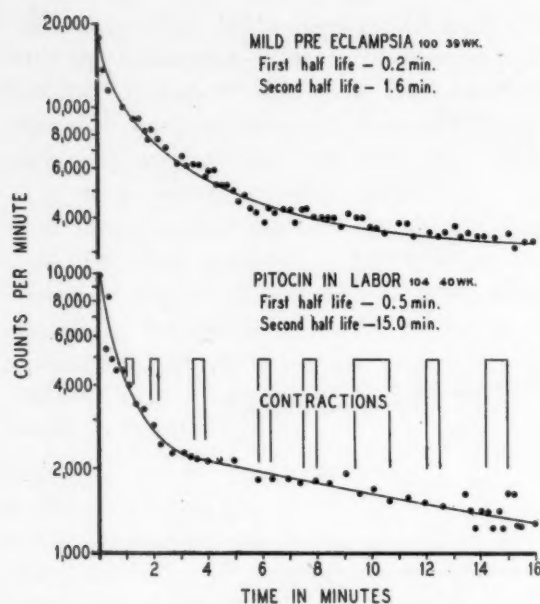


Fig. 6. The clearance during Pitocin-stimulated labor does not vary from the pattern one week prior to labor.

instances when there was a typical flat line. One of the two showed marked fetal distress with meconium-stained amniotic fluid. The baby was normal and well. In almost all the curves there was a rapid dip in the clearance at the onset of the contraction, then a leveling off. Fig. 5 shows this characteristic pattern.

Four patients in active labor at the time of the clearance received intravenous Pitocin. The cervix was fully effaced at 2 and 5 cm. dilatation. The characteristics of the clearance were no different from those of a normal labor. In several instances clearances have been obtained late in the third trimester and also during the course of labor. In clearance curves 100 and 104 (Fig. 6), although the half-life time during labor is relatively unchanged from that before labor, the period of normal clearance is shorter in duration during the course of labor. It is obvious that the same characteristic curve is obtained prior to and during the labor in the same patient.

In this group of patients in labor there were 3 with some type of toxemia, 2 with essential hypertension, and one with pre-eclampsia. These patients showed normal

clearances during labor and had normal babies. During labor the clearance curves are generally normal. Only one determination showed an abnormal curve and a normal clinical course. The other flat clearance was associated with fetal distress.

**Supine hypotension.** Five patients showed typical supine hypotension during the sodium clearance. These patients were started in the supine position and during the clearance they complained of dizziness and weakness. Blood pressure readings indicated levels between 90/55 and 60/30. During the period of mild shock, the clearance curve is of a flat type, and, as soon as the patient is turned on her side, the curve drops rapidly in the normal fashion. As shown in Fig. 7, Patient 108 demonstrates this characteristic pattern.

During sodium clearance in 5 patients, concomitant sodium<sup>24</sup> blood levels were obtained. It was found that there was a rapid increase in the sodium level in the blood, and in the normal patient this reached its maximum at about 8 minutes. From that point on, there was a gradual diminution in the sodium level of the blood. This would indicate that at the commencement of the clearance there was a rapid build-up of the sodium in the blood and this was associated with the most rapid part of the clearance curve. The end portion of the clearance, or the plateau portion, represented the over-all level of sodium which was maintained for a number of hours in the blood stream. This study demonstrates that the maximum blood level of sodium occurs at the end of the rapid fall of the uterine wall clearance. In Patient 77, the maximum blood level occurs at 8 minutes, which is at the end of the rapid fall of the clearance curve, and in Patient 81 the maximum blood level is at 3.8 minutes, which is again at the time of maximum descent of the curve. Fig. 8 shows the uterine clearance and the blood levels obtained in Patient 81.

Associated with the clearances in three instances, a second scintillating counter was placed over the heart to determine the up-

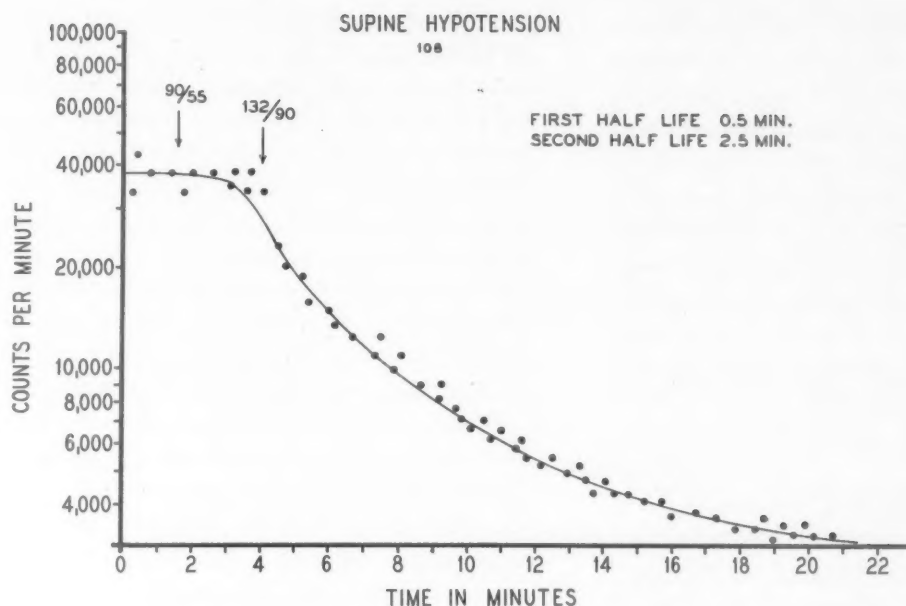


Fig. 7. Supine position in this clearance results in hypotension and a flat line. The lateral position returns the blood pressure to normal and the clearance reverts to a normal type.

take of sodium by the blood. As in the blood sodium levels, the scintillating counter recordings reached their maximum at the end of the rapid clearance.

Further analysis of our data demonstrated the frequency of an initial flat period in the clearance curve, particularly in the abnormal patient. In the normal patient exhibiting supine hypotension, the flat period as well as the hypotension may be corrected by turning the patient on her side. In unequivocal normal pregnancies, flat periods were rare and short, occurring in 15 per cent of the group. In toxemia and fetal distress, although the half-life clearance time was under 6 minutes, 32 and 67 per cent, respectively, had a flat period to commence the clearance curve. In these three categories—normal, toxemia, and fetal distress—all with abnormal half-life time had a high percentage of clearances with flat initial periods, as shown in Table III. The most significant portion of the clearance is the initial period.

We may also classify the data with respect to both clearance time and initial flat

period in the total group (Table IV). We observe that while 70 per cent of the normal group have clearance times less than 6 minutes and no initial flat period, the corresponding percentages are only 41, 17, 37, and 11 for the mild toxemia, severe tox-

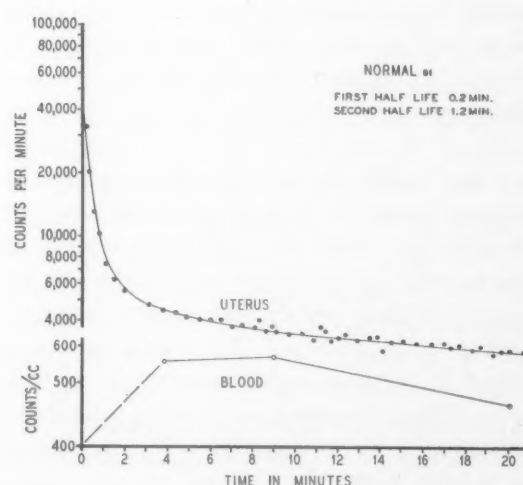


Fig. 8. The Na<sup>24</sup> blood level rises rapidly associated with the maximum fall of the uterine clearance curve. The blood counts reach a maximum as the clearance curve levels off at the background equilibrium.

**Table III.** Clearances with initial flat periods

Group	No. of normal clearances	Initially flat (%)	No. of abnormal clearances	Initially flat (%)
Normal	47	15	10	60
Toxemia	22	32	18	83
Fetal distress	3	67	6	100

**Table IV.** Clearance time and per cent initially flat

Group	Normal clearances (%) (no flat period)	Abnormal clearances (%) (with flat period)
Normal	70	11
Mild toxemia	41	29
Severe toxemia	17	83
Combined toxemia	37	37
Fetal distress	11	67

emia, combined toxemia, and fetal distress groups, respectively. Some discriminating power of the sodium clearance test is thus apparent, particularly between the normal group and the groups with severe toxemia and fetal distress.

Repeat clearances were performed in 10 patients, and 2 of these had a third clearance. In all instances, the half-life times were reduplicated, and in 9 cases the curves appeared similar. In several instances where there was progression in toxemia, the same form of the curve took on a slower fall and a longer initial flat period. The fact that the patient could be almost recognized by the slope of the curve is a significant feature of the accuracy of the injection into the uterine muscle. Repeat tests produced no complications; progression of the clearances was noted in patients with exacerbation of toxemia. These two findings are important observations suggesting that this technique may have some practical use.

#### Comment

At the present time the various clinical signs and symptoms of toxemia appear too

inadequate to depict accurately the objective findings in the uterus. All too frequently, in a patient in the last trimester with a minimal elevation of blood pressure, moderate edema, or a trace of proteinuria, sudden intrauterine death of the fetus will occur. It was hoped initially that a uterine muscle clearance might provide some additional information to permit more accurate identification of a fetus in danger of intrauterine death. Aside from initial work by Flexner and associates<sup>4</sup> on the transfer of sodium to the fetus, until now, three methods have been used by investigators. Initially, Browne and Veall<sup>2</sup> injected the Na<sup>24</sup> into the uteroplacental bed. This was only an experimental approach because of the difficulty in localizing the placenta. Johnson and Clayton<sup>7</sup> injected the Na<sup>24</sup> intravenously and then determined the radioactive pick-up over the uterus. The dosage was high and the isotope could go throughout the body in equal quantities. If the placenta were on the posterior wall, this reduced the pick-up. Actually, this test measured in a very gross manner the blood flow to the uterus, but the position of the placenta varied so greatly that the counting might be inaccurate.

The simplest method appeared to be that of Morris, Osborn, and Wright,<sup>11</sup> who used small doses of Na<sup>24</sup> directly into the muscle of the anterior uterine wall. The ideal position for injection was just below the umbilicus and lateral to avoid blood vessels, the bladder, and bowel. With use of a large two-inch sodium crystal and a scaler, it has been possible to reduce the dose for the test to 0.7 to 0.8  $\mu$ c in 0.5 c.c. of normal saline. The finest gauge spinal needle with stylet, 23 gauge, appeared most practicable for the procedure. With a little practice, not much difficulty was experienced after our first 20 clearances. No complications such as hemorrhage, infection, or injury to the baby have resulted.

Following the work of Flick, Shettles, and Taylor,<sup>5</sup> who injected the Na<sup>24</sup> into the non-pregnant cervix via the vagina, we attempted in 75 patients to study Na<sup>24</sup> in-



jected into the cervix during pregnancy. No significant differences were obtained in the normal and abnormal pregnancies in the last trimester.

Following this, the present series of tests was undertaken. After an evaluation of the entire series, it was decided that a clearance half-life of 6 minutes or longer was to be considered abnormal. Anything shorter was considered normal. Our choice of a 6 minute criterion was prompted by the following consideration: the distribution of half-life clearance times for the cases diagnosed clinically as normal has a mean of 2.5 minutes and a standard deviation of 2.9 minutes. This compares with a mean and standard deviation of 5.3 and 6.2, respectively, for the toxemia group as a whole. (A few clearances having an almost completely flat curve throughout were omitted since their half-life clearance times cannot be reliably measured.)

A statistical test for the difference of two means at the 1 per cent significance level reveals that for the toxemia group the mean clearance time is significantly higher than that for the normal group. However, there is considerable overlapping between the distributions. Hence, any threshold criterion (such as if the half-life is less than 6, the clearance is considered normal) cannot act to separate perfectly the normal patients from those with toxemia. At best a sensible choice can be made, such as 6, which classifies both a clinically normal patient as having a normal clearance and a toxemic patient as having an abnormal clearance a reasonably high percentage of the time. Any attempt to change the cut-off level between what constitutes a normal as opposed to an abnormal clearance only increases the detection power of one at the expense of the other. The use of 6 gives a good balance when all cases are considered.

The choice of a 6 minute criterion is reinforced by the fact that the distribution of half-life clearance times for the normal group is composed of two basically different parts: a lower distribution ranging from 0.1 to 6 minutes and a higher one ranging from

9.0 minutes upward. The higher distribution appears to be generated by unusual factors. In 50 per cent of the clearances comprising this distribution unusual factors (discussed previously in the paper) were associated with the patients involved. The lower distribution has a mean of 1.7 minutes and a standard deviation of 1.6 minutes, and consequently a mean plus-3 standard deviation value of 6.5. Thus, a threshold choice of 6 minutes seems a sensible choice in that the probability of obtaining a clearance time beyond 6 that belongs to the lower distribution is small.

All investigators have chosen between 6 and 8 minutes as the normal limit. It is of interest that, in the so-called normal group, 18 per cent had abnormal clearances. This compares similarly with the findings of Taylor and associates,<sup>14</sup> who had 23 per cent, or 11, with abnormal clearances. As our level of normal half-life is discretionary, so is our level of so-called clinical normal. In general, considering that errors may be made in either direction, 82 per cent normal pregnancies and clearances would appear to be significant in view of the fact that only 55 per cent of the group with toxemia had normal clearances. While 55 per cent is still a relatively high portion, it is to be remembered that the majority of toxemic patients in this series have the mild variety, which is well controlled, and they attend the clinic at weekly intervals. Those with severe toxemia almost uniformly had abnormal clearances.

Formal statistical corroboration of the significance of the 82 per cent normal clearance figure (less than 6 minutes) for the clinically normal group and the 55 per cent normal clearance figure for the group with toxemia is afforded by applying a chi-square test for statistical independence. When this is done, the test rejects the null hypothesis that the clinical diagnoses and clearance classifications are independent at the 1 per cent level of significance. In other words, the chi-square test indicates that the clearance times are dependent on the clinical diagnoses. However, the 55 per cent

figure is too high relative to the 82 per cent figure to establish a strong dependency. Of course, we must remember that 85 per cent of the cases of toxemia in this study are mild. While the  $\text{Na}^{24}$  clearance test is not a good discriminator between the normal group and that with mild toxemia, it is a stronger discriminator between the normal group and that with severe toxemia or fetal distress. Thus, Table II reveals that, while 82 per cent of the normal group had normal clearances, only 17 and 33 per cent of the groups with severe toxemia and fetal distress, respectively, had normal clearances. In addition, while only 23 per cent of the normal group had an initial flat period, 83 and 89 per cent of the groups with severe toxemia and fetal distress, respectively, had initial flat periods. Thus, long clearance times and initial flat periods serve to distinguish reasonably well between the normal group and the groups with severe toxemia and fetal distress, but with only small success between the normal group and the group with mild toxemia. Of course, we recognize that the sample sizes for the groups with severe toxemia and fetal distress (6 and 9, respectively) are small so that more experimental cases in these categories would be desirable.

In several instances repeat clearances associated with toxemia showed continued high half-lives and a progression in the abnormality as term approached. Although pre-eclampsia, hypertension, and superimposition are small groups in our series (23, 13, and 4, respectively) the percentage of abnormal clearances varies from 43 to 50 per cent. In general, those patients with toxemia who had no severe exacerbation of the condition had normal clearances. The presence of a prolonged clearance and toxemia, in general, was a signpost heralding further complications such as fetal distress, undersized infant, or fetal death.

The group demonstrating overt fetal distress showed the highest abnormal half-life rate. In 6 of the 9 there was an abnormal clearance curve and, in 8, an initial plateau period. Many of these clearances were ob-

tained prior to labor and some were repeated once. One was repeated on two occasions. The finding of abnormal clearances associated with fetal distress confirms the report of Wright and associates,<sup>15</sup> who showed a prolonged half-life of over 12 minutes during labor. The characteristic flat period was associated with almost all clearances in patients who exhibited fetal distress. The fact that the clearance was prolonged and flat prior to the onset of labor indicates that an abnormality in local diffusion of  $\text{Na}^{24}$  existed at an earlier date. The added effect of labor is sufficient to produce the signs of fetal distress. The addition of labor generally produced no significant increase in abnormal clearances. Four patients in labor receiving intravenous Pitocin demonstrated a normal clearance pattern.

Dieckmann and Pottinger<sup>3</sup> and, more recently, Plentl and Gray<sup>13</sup> have shown an increase in sodium space in acute toxemia. The latter found a 12 per cent increase in the sodium space when calculated as per cent of total body water. This finding may be of some significance in the prolongation of the half-life clearance time in the group with acute toxemia. Hawkins, Nixon, and Whyley<sup>6</sup> described the changes in electrolyte composition of the myometrium at the time of cesarean section. In pre-eclampsia there is an increase in extracellular fluid as well as an increase in both intracellular and extracellular sodium. This may in part explain the delayed  $\text{Na}^{24}$  clearance in toxemia.

The flat period associated with postural supine hypotension indicates that the local extracellular tissue diffusion is subjected to extremely rapid interference when hypotension occurs associated with postural change. The dramatic fall in the clearance curve when the patient turns on her side shows the close relationship between the local uterine extracellular space and the general circulation. Both  $\text{Na}^{24}$  blood levels and a second crystal over the heart demonstrate the rapid passage of the radioactive cation into the circulation. The blood stream level

and the local fall of the Na<sup>24</sup> are in a reciprocal relationship. Although this muscle clearance does not measure the blood flow directly, the local diffusion rate from the uterine muscle to the blood stream appears to bear an important relationship to the functional state of the uterine muscle. The uterine muscle clearance as performed in this study uses less radioactive material than previously. The extent of the correlation between normal and abnormal states in the late third trimester and its relative safety suggest that this test may be valuable in evaluating uterine muscle function.

### Conclusions

1. Na<sup>24</sup> may be accurately injected repeatedly into the myometrium without undue risk.
2. The radiation exposure to the patient is far below the maximum permissible dose.
3. The half-life values may be obtained from the clearance curve on semilogarithmic paper.
4. The data indicate that a half-life clearance time of 6 minutes may be used as a criterion to distinguish between normal and abnormal pregnancies. Thus, clearance times less than 6 minutes are considered normal and those 6 minutes or over abnormal.
5. High half-life clearance times and fre-

quent initial flat periods are characteristic of the groups with severe toxemia and fetal distress and serve to distinguish reasonably well between these and the normal group, which tends to have low clearance times without initial flat periods. The sample sizes for the groups with severe toxemia and fetal distress are small.

6. High half-life clearances and the presence of initial flat periods are also more prevalent in the group with mild toxemia than in the normal group. However, the incidence of these characteristics in the group with mild toxemia relative to the incidence in the normal group is not sufficiently high to indicate much success in distinguishing between patients with mild toxemia and normal patients.

7. Progression or superimposition of toxemia is followed by a prolongation of the clearance time.

8. The labor clearance curve is similar to the late pregnancy clearance. In true labor, V dips are frequent at the time of the contraction. Pitocin stimulation does not change the character of the curve.

9. Supine hypotension produces an abnormal clearance which may be rectified by a change in position.

10. Na<sup>24</sup> blood levels and heart counts indicate a rapid taking up of the Na<sup>24</sup> by the blood stream.

### REFERENCES

1. Apgar, V.: *Anesth. & Analg.* 32: 260, 1953.
2. Browne, J. C., and Veall, N.: *J. Obst. & Gynaec. Brit. Emp.* 60: 141, 1953.
3. Dieckmann, W. J., and Pottinger, R.: *AM. J. OBST. & GYNEC.* 74: 816, 1959.
4. Flexner, L. B., Cowie, D. B., Hellman, L. M., Wilde, W. S., and Vosburgh, G. J.: *AM. J. OBST. & GYNEC.* 55: 469, 1948.
5. Flick, F. H., Shettles, L. B., and Taylor, H. C., Jr.: *AM. J. OBST. & GYNEC.* 71: 1176, 1956.
6. Hawkins, D. F., Nixon, W. C. W., and Whyley, G. A.: *J. Obst. & Gynaec. Brit. Emp.* 67: 911, 1958.
7. Johnson, T., and Clayton, C. G.: *J. Obst. & Gynaec. Brit. Emp.* 62: 513, 1955.
8. Johnson, T., and Clayton, C. G.: *Brit. M. J.* 1: 312, 1957.
9. Kety, S. S.: *Am. Heart J.* 38: 321, 1949.
10. Moore, P. T., and Myerscough, P.: *J. Obst. & Gynaec. Brit. Emp.* 64: 207, 1957.
11. Morris, N., Osborn, S. B., and Wright, H. P.: *Lancet* 1: 323, 1955.
12. Morris, N., Osborn, S. B., Wright, H. P., and Hart, A.: *Lancet* 2: 481, 1956.
13. Plentl, A. A., and Gray, M. J.: *AM. J. OBST. & GYNEC.* 78: 472, 1959.
14. Taylor, E. S., Bruns, P. D., Hepner, H. J., and Drose, V. E.: *AM. J. OBST. & GYNEC.* 76: 983, 1958.
15. Wright, H. P., Morris, N., Osborn, S. B., and Hart, A.: *AM. J. OBST. & GYNEC.* 75: 3, 1958.



# Glutamic oxalacetic transaminase and lactic dehydrogenase in pregnancy

MARTIN L. STONE, M.D.

MIRIAM LENDING, M.D.

LAWRENCE B. SLOBODY, M.D.

JOAN MESTERN

*New York, New York*

SINCE 1954 there has been marked interest in the enzyme systems with particular emphasis on glutamic oxalacetic transaminase (GOT) and lactic dehydrogenase (LDH). Changes in the activity of these enzymes are of diagnostic and prognostic value in a variety of diseases including hepatitis, myocardial infarction, and cerebral vascular accidents.

More recently, attention has been directed to studies of these enzyme systems in pregnancy. Most investigators are in agreement that GOT levels are unchanged in normal pregnancy.<sup>1-4</sup> Early reports on LDH activity indicated an increase in normal pregnancy.<sup>5,6</sup> Except for the study by Hagerman and Wellington<sup>7</sup> which indicated a rise in LDH activity during the last 6 weeks of pregnancy, all other recent reports indicate that LDH activity is normal throughout normal pregnancy.<sup>8-11</sup> The smaller number of cases and the failure of some reports

to correlate the results with the duration of the pregnancy warrants further study of the activity of these enzymes in pregnancy.

Our own studies began with the determination of GOT and LDH activity not only in plasma but in the cerebrospinal fluid of newborn infants. Our findings, which are the subject of a previous report,<sup>12</sup> suggest that increases in cerebrospinal fluid enzyme activity may be useful in studying newborn infants with suspected intracranial pathologic conditions. Determinations of GOT and LDH are being made in a large group of pregnant women during all stages of normal and abnormal pregnancy so that the relationships between the levels in the mothers and their newborn babies can be studied.

The present report includes the results of a study of plasma GOT and LDH activity obtained in a group of 113 women in normal pregnancy to establish the normal range of enzyme activity. A subsequent report will include patients with complications of pregnancy with particular emphasis on toxemias. A third report will correlate the findings in mothers and newborn infants.

## Material and methods

The 113 women comprising the study group included 19 in the first trimester, 26 in the second trimester, 26 in the third trimester, 19 in the intrapartum period, and 23 who were 6 weeks post partum.

*From the Departments of Pediatrics and Obstetrics and Gynecology and the Laboratory of Maternal-Newborn Research, New York Medical College, Flower and Fifth Avenue Hospitals.*

*This study was supported in part by Research Grant No. 3B-9024, National Institute of Neurological Diseases and Blindness, United States Public Health Service, and by a grant from the Committee on Research, Council on Pharmacy and Chemistry, American Medical Association.*

Table I. Plasma GOT and LDH activity of normal women

Period	GOT (U./ml./min.)*			LDH (U./ml./min.)†		
	No. of cases	Range	Average and standard deviation	No. of cases	Range	Average and standard deviation
First trimester	19	5.3-32	13.5 ± 6.7	19	160-1,490	499 ± 318
Second trimester	26	5.0-34	14.4 ± 8.4	26	70-1,590	360 ± 326
Third trimester	26	3.0-42	14.7 ± 9.5	26	95-1,160	537 ± 307
Intrapartum	19	4.0-38	12.1 ± 7.9	16	280-1,820	476 ± 357
Postpartum (6 weeks)	23	9.0-32	17.9 ± 7.0	22	150-1,490	786 ± 432
All maternal assays	113	3.0-42	14.6 ± 8.3	109	70-1,820	529 ± 380

\*Normal, 5-40.

†Normal, 260-850.

Heparinized blood samples were obtained in all cases, centrifuged at 3000 r.p.m., and separated immediately. The plasma was kept frozen and all determinations were performed within 7 days. GOT activity was determined by the method of Karmen<sup>13</sup> (normal range of activity, 5 to 40 units per milliliter per minute) and LDH activity by the method of Wroblewski and LaDue<sup>14</sup> (normal range of activity, 260 to 850 units per milliliter per minute). All determinations were performed at 25° C. with a Beckman DU spectrophotometer. The activity is expressed as units per milliliter per minute. One unit equals a decrease in optical density of 0.001 divisions per milliliter plasma per minute.

### Results

The range, mean values, and standard deviation of the GOT and LDH activity in 90 normal pregnant women and 23 women 6 weeks post partum are illustrated in Table I. A review of the GOT activity in individual cases (Fig. 1) reveals that the activity throughout pregnancy, during delivery, and 6 weeks post partum is normal and in general lower than that reported in normal nonpregnant individuals. The LDH activity (Fig. 2) shows an elevation in 3 of 19 cases studied in the first trimester, 2 of 26 cases in the second trimester, and 4 of 26 cases in the third trimester. Of the total antepartum study group of 71 cases, LDH activity was elevated in 9. Only 1 of 16 patients studied in the intrapartum period

showed an elevation. In the postpartum period, however, 11 of 22 cases showed a definite increase in LDH activity.

### Comment

The present report on a series of 113 pregnant women is a preliminary study to determine normal activity of GOT and LDH during all stages of pregnancy, including the intrapartum and postpartum periods, in order to establish a base line for the evaluation of complications of pregnancy and delivery. The possibility that changes could be determined early in the mother which might indicate future complications in the newborn infant was considered.

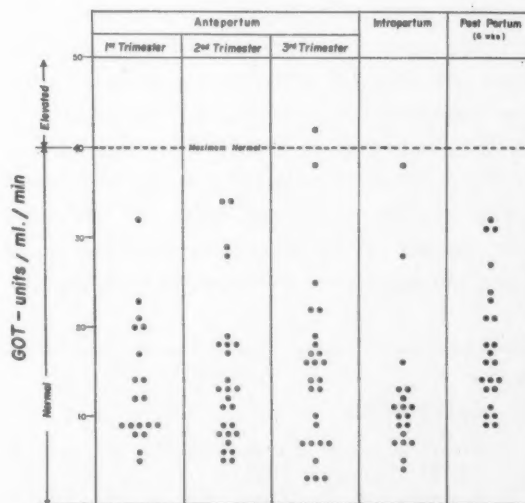


Fig. 1. GOT activity in individual cases.

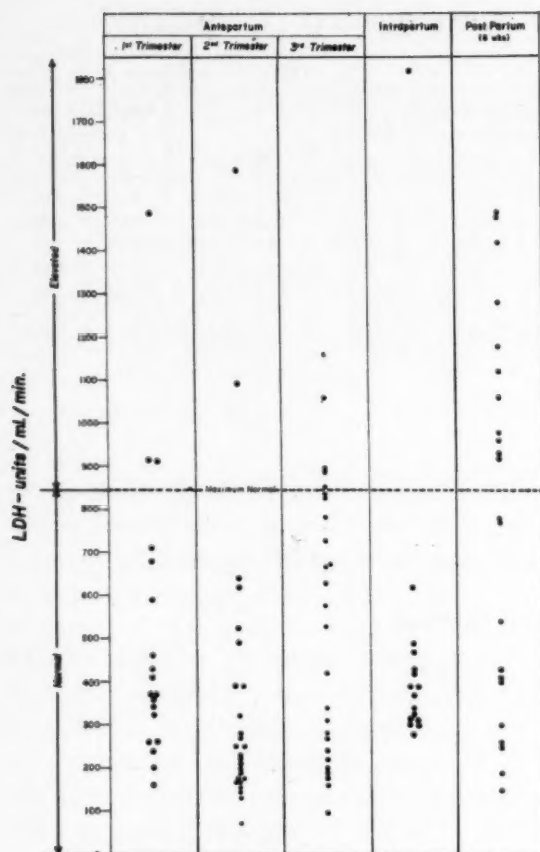


Fig. 2. LDH activity in individual cases.

The results of this study show no increase in GOT activity during the various stages in normal pregnancy. In fact, the activity was, as a rule, lower than usually noted in nonpregnant individuals. This has been previously reported,<sup>1</sup> and it has been suggested that the lowered activity is due to pyridoxine deficiency in pregnancy,<sup>15</sup> secondary to a disturbance in B<sub>6</sub> metabolism.<sup>16</sup>

Some increase in LDH activity was found (Fig. 2), but additional cases are necessary for proper statistical interpretation. The high percentage of patients who showed an

increased activity 6 weeks post partum seems to us to be significant. This increase in enzyme activity may be the result of involutional changes in the uterus and increased protein catabolism associated with the puerperium. Smith and his co-workers<sup>10</sup> reported that the LDH was uniformly elevated in a series of 15 postpartum patients. This is a direct variance with the result reported by Holmes and associates<sup>17</sup> on 20 postpartum patients.

The studies of enzyme activity in pregnancy are too new to allow for firm conclusions. The results as determined in this series of normal pregnancies will be correlated with the findings in women with complicated pregnancies and with the findings in newborn infants delivered following both normal and abnormal pregnancies. It is hoped that additional information will be forthcoming from other investigators in this field.

### Summary

1. The GOT and LDH levels were studied in 113 women in all three trimesters of pregnancy, the intrapartum period, and 6 weeks post partum.

2. No elevations in GOT activity were found in any of the patients. Often the levels were lower than the average for non-pregnant women.

3. LDH activity was generally normal with a slight increase seen in a small number of patients.

4. At the time of the 6 weeks postpartum check-up, there was an increase in LDH activities in 11 of 22 patients.

5. This and other studies would seem to indicate that in normal pregnancy serum GOT activity is within normal limits but LDH activity may be increased.

### REFERENCES

1. West, M., and Zimmerman, H. J.: *Am. J. M. Sc.* 235: 443, 1958.
2. Knutson, R. G., Cornatzer, W. E., Moore, J. H., and Nelson, W. W.: *J. Lab. & Clin. Med.* 51: 773, 1958.
3. Borglin, N. E.: *J. Clin. Endocrinol.* 18: 872, 1958.
4. Crisp, W. E., Miesfeld, R. L., Frajola, W. J.: *Obst. & Gynec.* 13: 487, 1959.
5. Hill, B. R., and Levi, C.: *Cancer Res.* 14: 513, 1954.



6. Hill, J. H.: *J. Nat. Cancer Inst.* **18**: 307, 1957.
7. Hagerman, D. D., and Wellington, F. M.: *Am. J. Obst. & Gynec.* **77**: 348, 1959.
8. Brody, S.: *Acta endocrinol.* **25**: 101, 1957.
9. Little, W. S.: *Obst. & Gynec.* **13**: 152, 1959.
10. Smith, J. J., Schwartz, E. D., and Schwartz, M. K.: *Obst. & Gynec.* **13**: 163, 1959.
11. Linton, E. B., and Miller, E. C., Jr.: *Am. J. Obst. & Gynec.* **78**: 11, 1959.
12. Lending, M., Slobody, L., Stone, M. L.: *Pediatrics* **24**: 378, 1959.
13. Karmen, A.: *J. Clin. Invest.* **34**: 131, 1955.
14. Wroblewski, F., and LaDue, J. S.: *Proc. Soc. Exper. Biol. & Med.* **90**: 210, 1955.
15. Glendening, M. B., Cohen, A. M., and Page, E. W.: *Proc. Soc. Exper. Biol. & Med.* **90**: 25, 1955.
16. Wachstein, M., and Gudaitis, A.: *J. Lab. & Clin. Med.* **40**: 550, 1952.
17. Holmes, D. E., Dillon, R. F., and Powell, D. V.: *Obst. & Gynec.* **12**: 477, 1958.

# Creatinine transport between baby and mother at term

HARRY S. McGAUGHEY, JR., M.D.

E. L. COREY, Ph.D.

WILLIAM A. SCOGGIN, M.D.

CONWAY H. FICKLEN, M.D.

W. NORMAN THORNTON, JR., M.D.

*Charlottesville, Virginia*

THE mechanisms for the exchange of solute and water between the maternal and fetal bodies during human pregnancy have been the subject of many articles during the past several years.<sup>1-9</sup> In prior reports<sup>10-11</sup> from this laboratory, evidence was presented suggesting that the chorioamnion constituted a route, in addition to the placental site, for fetomaternal exchange of water and urea. These studies suggested that water and urea were excreted by the fetus into the amniotic cavity and returned to the maternal fluids by passive diffusion across the chorioamnion in response to a concentration gradient.

The present report is a continuation of these studies with use of creatinine as the test substance, since its concentration is said to be higher in the amniotic fluid than in either maternal or fetal sera,<sup>12-14</sup> a circumstance indicative of a secretory process across the chorioamnion from maternal tissue to amniotic cavity or of fetal excretion into the amniotic fluid, with equilibration being limited by the diffusion characteristics of the membrane.

*From the Departments of Obstetrics and Gynecology and Physiology, School of Medicine, University of Virginia.*

*This investigation was supported in part by a research grant (H-2620-C2) from the National Heart Institute, United States Public Health Service.*

As in the urea study, the present investigation consisted of two principal divisions. In the first, the concentrations of creatinine in maternal sera obtained from the antecubital vein, brachial artery, and placental pool, in fetal sera from the umbilical artery and vein, and in amniotic fluid were determined to characterize the state of equilibrium present in vivo across the placental barrier and the chorioamnion. The second aspect of the study pertained to in vitro experiments designed to assess the transport kinetics of the chorioamnion for creatinine.

## Methods

All in vivo samplings were performed during term delivery. The amniotic fluid samples were obtained by either transabdominal or transvaginal aspiration of the amniotic sac. In those few instances during the study where the placental pool was accessible for transabdominal aspiration, a sample from this site was included.<sup>9</sup> Immediately upon completion of the second stage of labor and prior to cord ligation, blood samples were drawn from the umbilical artery and vein by needle aspiration. In conjunction with these samplings, blood was drawn from the maternal brachial artery and antecubital vein.

The in vitro experiments were performed as follows: immediately after completion of the third stage of labor a disc of chorio-

amniotic membrane (approximately 40 sq. cm.) was excised and suspended over the open end of a small (150 ml.) Plexiglas chamber. This chamber was then inserted into a larger compartment as shown schematically in Fig. 1. In all experiments, the concentrations of glucose and the various salts of the Locke's solution bathing both sides of the membrane were identical. In the first series of experiments the concentration of creatinine on both sides of the membrane was likewise identical, whereas, in the second series, creatinine was added to the smaller compartment and an isosmotic equivalent of sucrose to the outer chamber. Thus, in all experiments an isosmotic state existed across the membrane. In one half of each series the membrane was oriented so that the amniotic surface was exposed to the solution in the small chamber, while in the remainder the orientation was reversed. The temperature was held constant at 37° C. and oxygenation, as well as agitation, of the solutions on both sides of the membrane was achieved by means of aeration with oxygen gas. At designated time intervals aliquots were drawn from both chambers for analysis.

A total of 617 determinations involving sera, amniotic fluid, and artificial media were performed with use of the Jaffe reaction, as outlined by Bonsnes and Taussky,<sup>15</sup> in a Coleman Jr. Spectrophotometer at a wavelength of 520 m $\mu$ .

### Results

To eliminate the variability in serum creatinine concentration from individual to individual, we elected to consider each mother and her products of conception as a unit. Thus, the concentration of creatinine present in each maternal arterial, placental pool, umbilical artery, and vein serum as well as in each amniotic fluid sample has been compared to that present in that particular parturient's antecubital venous sample. This mode of presentation further negates any masking of the results inherent in a multiple sampling problem in which it is impossible to obtain a sample from each site in every instance.

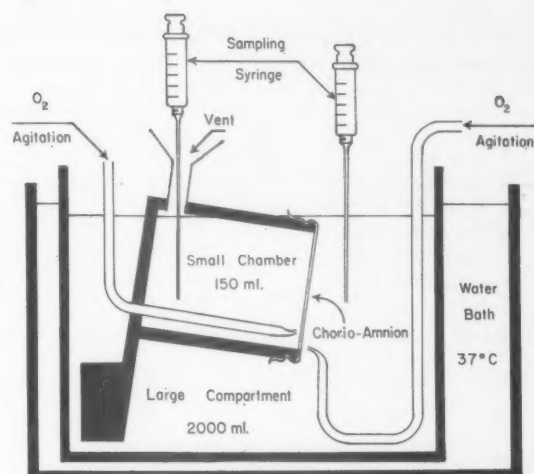


Fig. 1. Diagrammatic representation illustrating the method employed during *in vitro* studies of the permeability of the chorioamniotic membranes to creatinine.

In Table I the *in vivo* data obtained at 37 deliveries have been collated. The concentration of creatinine in the sera obtained from the maternal antecubital vein averaged 0.91 mg. per cent with a range of 0.57 to 1.37 mg. per cent. Table I demonstrates that creatinine is in equilibrium between the maternal and fetal bodies across the placental barrier but that its concentration is significantly higher in the amniotic fluid than in any of the vascular compartments sampled.

The data obtained in the *in vitro* experiments wherein the concentrations of creatinine, glucose, and the various ions of the Locke solution were identical on both sides of the membrane are depicted in Table II. The values presented are ratios derived by comparison of the concentration of creatinine at each time interval to that present at zero time. Statistical analysis indicates that the mean ratio does not deviate significantly from unity during the time interval of study.

Data obtained in the *in vitro* experiments in which creatinine was added to the solution (small chamber) bathing only one surface of the membrane are shown in Fig. 2. In these experiments an isosmotic state was maintained across the membrane by the addition of an isoequivalent amount of sucrose to the solution (large chamber) bathing the other



**Table I.** Comparison of creatinine concentrations in maternal and fetal sera and in amniotic fluid to that present in maternal peripheral venous serum\*

<i>Serum</i>	<i>No. of samples</i>	<i>Mean ratio</i> <i>(sample</i> <i>maternal venous)</i>	<i>Standard deviation</i>	<i>Significance of deviation of the mean ratio from unity†</i>
Maternal artery	23	0.99	±0.08	None
Placental pool	9	1.00	±0.09	None
Umbilical vein	35	1.00	±0.11	None
Umbilical artery	20	1.02	±0.10	None
Amniotic fluid	19	2.92	±0.80	Highly significant

\*Mean creatinine concentration (37 determinations) in maternal peripheral venous serum: 0.91 ± 0.19 mg. per cent.

† $t = \frac{\sqrt{N}(\bar{X} - 1.00)}{\sqrt{\frac{\sum (X - \bar{X})^2}{N - 1}}}$  where  $X$  = individual determination,  $\bar{X}$  = mean of  $X$ , and  $N$  = number of samples.

surface. The decreasing concentration of creatinine within the smaller chamber is expressed as a logarithmic plot of the percentages of the creatinine present at zero time. The solid circles refer to the mean value for each time period in which the amniotic surface of the chorioamnion faced the solution containing the creatinine, while the open circles refer to the mean data for the experiments in which the membrane orientation was reversed. The bar graphs indicate one standard deviation from the mean. At each time interval the difference between the two means was calculated and the figure in parenthesis is the determined "t" value.\* The straight line is the regression line calculated by the method of least squares<sup>16</sup> for all of the experimental values (slope  $1.98 \times 10^{-4}$ ).

#### Comment

The circumstance that creatinine is in equilibrium at term between the maternal and fetal bodies across the placental site suggests that the placenta may not be required to excrete creatinine derived from creatine metabolism in the fetus. The further observation that the concentration of creatinine in the amniotic fluid exceeds that in either the maternal or the fetal sera suggests that am-

niotic fluid may represent a repository for fetal excretory creatinine.

The conclusion that amniotic fluid creatinine is primarily derived as a metabolic waste from the fetus requires for its final confirmation precise knowledge as to the excretory capabilities of the fetus in utero. At the present time this facet is technologically unassessable in the human. In vitro experimentation, however, permits the transport capabilities of the chorioamnion to be assessed. Several studies<sup>17-19</sup> have suggested that the chorioamnion possesses a secretory potential, and an active secretory process would constitute a possible mechanism accounting for an increased creatinine content in the amniotic fluid as compared to maternal and fetal sera.

In the initial series of in vitro experiments (Table II), the membrane was placed between two solutions of identical creatinine concentration. Any alteration in concentration would be indicative of an active process as it would indicate transport against a concentration gradient. Since no net change in concentration regardless of membrane orientation was detectable during the interval of study, a unidirectional excretory mechanism in either the chorionic or the amniotic layer of the membrane seems unlikely, unless such transport be associated with the transport of an isoequivalent amount of water. The latter consideration would, however, not explain the in vivo observations. In the second series of in vitro experiments the membrane was placed between two isosmotically

\*Significance of difference between means:

$$t = \frac{m^1 - m^2}{\sqrt{\left(\frac{SD_{m^1}}{\sqrt{N_{m^1}}}\right)^2 + \left(\frac{SD_{m^2}}{\sqrt{N_{m^2}}}\right)^2}}$$

where  $m^1$  and  $m^2$  refer to the respective mean values,  $SD_{m^1}$  and  $SD_{m^2}$  to the standard deviation from the means, and  $N_{m^1}$  and  $N_{m^2}$  to the number of individual samples comprising the means. The number of degrees of freedom equals the total number of samples minus two.

Figure 1 is a line graph showing the  $\text{Log}_{10}$  Percent Initial Concentration of amphetamine and chorion over time (0, 30, 60, 90, 120, 150 minutes). The y-axis ranges from 1.96 to 2.00. A solid line represents the mean concentration, which decreases over time. Error bars represent the standard deviation (S.D.). Data points are labeled with p-values in parentheses: (0.118) at 0 min, (0.813) at 30 min, (0.784) at 60 min, (0.432) at 90 min, (0.631) at 120 min, and (0.607) at 150 min. A legend indicates that solid circles and open circles represent the mean, while open and solid rectangles represent the S.D. for Amnion and Chorion respectively. An asterisk (\*) indicates the 'T' value.

Time (min)	Mean (Amnion)	S.D. (Amnion)	Mean (Chorion)	S.D. (Chorion)	p-value
0	~1.995	~0.005	~1.995	~0.005	(0.118)
30	~1.995	~0.005	~1.995	~0.005	(0.813)
60	~1.992	~0.005	~1.992	~0.005	(0.784)
90	~1.988	~0.005	~1.988	~0.005	(0.432)
120	~1.978	~0.005	~1.978	~0.005	(0.631)
150	~1.970	~0.005	~1.970	~0.005	(0.607)

Denying a secretory function to the membrane, the second series of *in vitro* experiments further permits the specific rate constant ( $k_1$ ) to be calculated by determination

[illegible]

of the slope of the regression line by the method of least squares;  $k_1$  so determined has a value of  $4.54 \times 10^{-4} \text{ min.}^{-1}$ .

Application of this specific rate constant determined by in vitro techniques to the circumstances found in vivo permits the approximate order of magnitude for creatinine transport from amniotic to maternal fluids across the intact chorioamnion to be estimated. This calculation requires the assumption that the amniotic fluid at term is in a steady state (the concentration gradient for creatinine between amniotic fluid and maternal blood being relatively constant in an individual, although varying from one individual to another). It further requires an estimation of the effective surface area of the intact chorioamnion—approximately 900 sq. cm., eliminating the area in juxtaposition to the placenta.<sup>21</sup> The equation for estimating creatinine transport would, therefore, be  $\dot{Q} = V k_1 t C \frac{(A^I)}{A^E}$  where  $\dot{Q}$  represents the quantity of creatinine diffusing per day;  $V$  is the volume (150 ml.) of solution in the small chamber;  $k_1$  is the specific rate constant;  $t$  is time in minutes;  $C$  is the concentration gradient of 1.75 mg. per cent (mean amniotic fluid minus mean maternal creatinine concentrations);  $A^I$  is the intact effective surface area of the chorioamnion (900 sq. cm.); and  $A^E$  is the surface area of the disc employed in the experiments (33.2 sq. cm.). Substitution of these particular values and solving for  $\dot{Q}$  indicates that 46.5 mg. of creatinine may be transferred from the amniotic to the maternal fluid per day. This

value constitutes a minimum, since it is based on a condition of isosmotic equilibrium across the membrane, whereas in vivo an osmotic gradient for water is present and any creatinine carried by the diffusion of water would be in addition to this estimate.

Comparison of this value to that obtained by Garby<sup>5</sup> suggests that his estimate of 0.01 Gm. per hour for the net transport of creatinine between amniotic cavity and maternal fluid may be an overapproximation since the diffusion characteristics of the chorionic layer of the chorioamnion were not included in his study.

### Summary

1. Evidence is presented on the basis of both in vivo and in vitro observations that the chorioamnion constitutes a route of transport for the equilibration of creatinine between maternal and fetal fluids in addition to that provided by placental exchange.

2. The data reported are interpreted as evidence that fetomaternal transfer of creatinine occurs solely by the process of diffusion.

3. That creatinine is present in amniotic fluid in increased concentration to that encountered in maternal serum is confirmed. This circumstance is attributed to the rate of deposition of creatinine in the amniotic fluid by the fetal tissues, coupled with the diffusion characteristics of the chorioamnion.

4. A minimal estimate of the daily amount of creatinine diffusing from amniotic to maternal fluids across the chorioamniotic membrane is presented.

### REFERENCES

1. Paul, W. M., Enns, T., Reynolds, S. R. M., and Chinard, F. P.: *J. Clin. Invest.* 35: 634, 1956.
2. Plentl, A. A., and Hutchinson, D. L.: *Proc. Soc. Exper. Biol. & Med.* 82: 681, 1953.
3. Brambell, F. W. R.: *Cold Spring Harbor Symp. Quant. Biol.* 19: 71, 1954.
4. Freda, V. J.: *AM. J. OBST. & GYNEC.* 76: 407, 1958.
5. Garby, L.: *Acta physiol. scandinav.* 40: suppl. 137, 1957.
6. Page, E. W., Glendening, M. B., Margolis, A., and Harper, H. A.: *AM. J. OBST. & GYNEC.* 73: 589, 1957.
7. Cox, L. W., and Chalmers, T. A.: *J. Obst. & Gynaec. Brit. Emp.* 60: 203, 1953.
8. Clemetson, C. A. B., and Churchman, J.: *J. Obst. & Gynaec. Brit. Emp.* 61: 364, 1954.
9. McGaughey, H. S., Jr., Jones, H. C., Jr., Talbert, L., and Anslow, W. P., Jr.: *AM. J. OBST. & GYNEC.* 75: 482, 1958.
10. McGaughey, H. S., Jr., Scoggin, W. A., Jones, H. C., Jr., Thornton, W. N., Jr., and Anslow, W. P., Jr.: *S. Forum* 9: 675, 1959.



11. McGaughey, H. S., Jr., Corey, E. L., Scoggin, W. A., Bobbitt, O. B., Jr., and Thornton, W. N., Jr.: *AM. J. OBST. & GYNEC.* 78: 844, 1959.
12. Makepeace, A. W., Fremont-Smith, F., Dailey, M. E., and Carroll, M. P.: *Surg. Gynec. & Obst.* 53: 635, 1931.
13. Plass, E. D.: *Bull. Johns Hopkins Hosp.* 28: 137, 1917.
14. Plass, E. D.: *Bull. Johns Hopkins Hosp.* 28: 297, 1917.
15. Bonsnes, R. W., and Taussky, H. H.: *J. Biol. Chem.* 158: 581, 1945.
16. Edwards, A. L.: *Statistical Methods for the Behavioral Sciences*, New York, 1955, Rinehart and Co., Inc.
17. Polano, O.: *Ztschr. Anat.* 63: 539, 1922.
18. Taussig, F. J.: *AM. J. OBST. & GYNEC.* 14: 505, 1927.
19. Danforth, D., and Hull, R. W.: *AM. J. OBST. & GYNEC.* 75: 536, 1958.
20. Snedecor, G. W.: *Statistical Methods*, Ames, Iowa, 1940, Iowa State College Press.
21. Reynolds, S. R. M.: *Physiology of the Uterus*, ed. 2, New York, 1949, Paul B. Hoeber, Inc.

# Serum lipids and protein-bound iodine levels of Guatemalan pregnant women from two different socioeconomic groups

JOSÉ MÉNDEZ, P.H.D.

NEVIN S. SCRIMSHAW, P.H.D., M.D., M.P.H.

MARVIN D. ABRAMS\*

EDWIN N. FORMAN\*

*Guatemala City, Guatemala*

NONPREGNANT women of upper socioeconomic status in Guatemala have been shown to have higher serum cholesterol levels than those in lower socioeconomic groups.<sup>1</sup> Serum cholesterol levels increased during pregnancy so that at term no significant difference was found between the serum cholesterol levels of the two groups,<sup>2</sup> despite the marked differences in dietary intake and cultural patterns. A greater rise of serum cholesterol thus occurred in the women of lower income status during pregnancy than in their upper income counterparts. The present study extends these observations to the development of hyperlipemia during gestation in the two groups and investigates a possible difference between them in thyroid function, as measured by protein-bound iodine.

*From the Institute of Nutrition of Central America and Panama (INCAP).*

*This investigation was supported in part by research Grant H-2653 from the National Heart Institute of the United States Public Health Service, and by funds from the Nutrition Foundation Inc.*

*INCAP Publication I-139.*

*\*Medical student Fellows of the National Foundation for Infantile Paralysis and the Williams-Waterman Fund of the Research Corporation.*

## Materials and methods

For the study of lipemia a total of 219 blood samples were collected, 163 from women in the prenatal clinic and maternity ward of the Roosevelt Hospital, a large charity institution in Guatemala City. They represented a lower socioeconomic stratum as judged from income status and an interview by a social worker. Seventeen were in the first trimester of pregnancy, 52 in the second, and 69 in the third; 25 women were studied at the time of delivery. The upper socioeconomic sample was made up of 56 women who attended private clinics and were wives of business and professional men in Guatemala City. Six were in the first trimester of pregnancy, 12 in the second, and 10 in the third; 28 were studied at delivery.

Protein-bound iodine (PBI) was also determined in the blood samples from all of the women studied at the time of delivery. For comparison, PBI determinations were done on blood samples obtained from two additional groups, one from lower income and the other from upper income families, each composed of 12 randomly selected nonpregnant women. Patients with abnormal pregnancies or parturitions were excluded, as well as patients with obvious thyroid

gland disease or previous iodine therapy. All blood samples were taken in the fasting state and protected from contamination with iodine.

Serum cholesterol was measured by the method of Abell and associates.<sup>3</sup> Lipid phosphorus was determined by the method of Maclay<sup>4</sup> adapted to a micro scale, and total lipids by the dichromate oxidation of Bragdon<sup>5</sup> in 0.05 ml. of serum with use of lipid extraction with Bloor's solvent mixture. The method of Grossmann and Grossmann<sup>6</sup> for the assay of protein-bound iodine was modified by stopping at a standard time of 10 minutes the catalytic reaction carried out at 25° C. with brucine.

### Results

In Table I the serum lipids and protein-bound iodine of the nonpregnant and pregnant women at delivery are presented. No significant differences in total serum lipids and PBI levels were found between the nonpregnant women of the two socioeconomic groups. Upper income nonpregnant women, however, had far more serum lipid phosphorus than lower income ones. The difference in cholesterol levels between nonpregnant women in the two socioeconomic groups was also significant; the upper income group showed the higher average. In the pregnant women at delivery no significant difference was observed in total lipids, lipid phosphorus, cholesterol, and protein-bound iodine for the two socio-

economic groups. If values for women at delivery are compared with those for nonpregnant women, a highly significant increase is observed for all serum lipid fractions and PBI ( $P < 0.001$  in all cases).

Lipid phosphorus and cholesterol levels for each trimester of pregnancy in both socioeconomic groups are given in Table II. For women in the lower socioeconomic group, these levels are shown in Table III for each month of pregnancy. There is a steady increase in lipid fractions during the course of pregnancy.

As shown in Table IV, highly significant positive correlations were found between cholesterol and total lipids in all of the groups studied and between total lipids and lipid phosphorus for the pregnant women at delivery in both socioeconomic groups. A highly significant positive correlation was also obtained between cholesterol and lipid phosphorus in the pregnant women at delivery in the upper income group. In the case of the pregnant women of the lower income group at delivery this correlation was significant at the 5 per cent level of probability. Significant correlations were also found between PBI and cholesterol and PBI and lipid phosphorus in women of the lower income group at delivery.

### Comment

One of the metabolic alterations of pregnancy is the increased activity of the thyroid gland as revealed by clinical studies showing

Table I. Serum lipid and protein-bound iodine concentration in nonpregnant and pregnant women in two socioeconomic groups in Guatemala City

Economic groups	Total lipids (mg./100 ml.)		Lipid phosphorus (mg./100 ml.)		Cholesterol (mg./100 ml.)		Protein-bound iodine (µg/100 ml.)	
	Upper	Lower	Upper	Lower	Upper	Lower	Upper	Lower
<i>Nonpregnant</i>								
Number studied	10	12	10	12	12	12	11	11
Mean	586	633	9.49	6.63	175	146	6.53	6.08
Standard deviation	89	97	1.96	1.47	41	20	1.13	0.63
<i>At time of delivery</i>								
Number studied	28	24	28	24	28	26	26	24
Mean	991	1,023	13.90	13.88	232	230	8.91	8.82
Standard deviation	124	150	2.04	2.30	37	42	1.31	1.43



**Table II.** Serum lipid phosphorus and cholesterol levels of pregnant Guatemalan women of two different socioeconomic groups

Socioeconomic groups	Lipid phosphorus (mg./100 ml.)			Cholesterol (mg./100 ml.)		
	No.	Mean	Standard deviation	No.	Mean	Standard deviation
<i>First trimester</i>						
Upper income	7	9.53	1.29	6	206	32
Lower income	17	9.36	1.46	17	170	36
<i>Second trimester</i>						
Upper income	12	10.97	1.83	12	208	44
Lower income	52	10.36	1.79	52	187	43
<i>Third trimester</i>						
Upper income	11	13.01	1.27	10	248	44
Lower income	69	11.63	1.85	69	210	49

**Table III.** Serum lipid phosphorus and cholesterol during the course of pregnancy in lower income Guatemalan women

Month of pregnancy	Lipid phosphorus (mg./100 ml.)			Cholesterol (mg./100 ml.)	
	No.	Mean	Standard deviation	Mean	Standard deviation
1	1	6.98	—	145	—
2	2	8.56	—	144	—
3	14	9.65	1.38	176	37
4	19	9.86	1.74	185*	33
5	11	10.40	1.85	190	35
6	23	10.76	1.78	196	35
7	24	11.22	0.95	197	27
8	16	11.69	2.66	222	66
9	29	11.94	1.89	215	51

\*No. = 18.

**Table IV.** Calculated correlations of the different variables

	Lower income women				Upper income women			
	Nonpregnant		Pregnant (at delivery)		Nonpregnant		Pregnant (at delivery)	
	Degrees of freedom	Correlation coefficient	Degrees of freedom	Correlation coefficient	Degrees of freedom	Correlation coefficient	Degrees of freedom	Correlation coefficient
Total lipids—lipid phosphorus	10	0.379	22	0.699*	8	0.617	26	0.637*
Cholesterol—total lipids	10	0.787*	21	0.661*	8	0.862*	25	0.771*
Cholesterol—lipid phosphorus	10	0.473	21	0.506†	8	0.360	25	0.509*
Cholesterol—PBI	9	-0.170	19	0.437†	9	-0.358	24	-0.069
PBI—lipid phosphorus	9	-0.494	17	0.497†	7	0.190	23	0.284
PBI—total lipids	9	-0.272	17	0.349	7	-0.330	23	0.022

\*Significant at the 1 per cent level.

†Significant at the 5 per cent level.

progressive thyroid enlargement during gestation,<sup>7</sup> laboratory investigations demonstrating elevated levels of serum protein-bound iodine and thyroxine,<sup>8</sup> greater uptake of radioactive iodine,<sup>9</sup> and histological evidence.<sup>8</sup> It is also known that proper thyroid function is dependent on the diet of the individual, particularly the intake of iodine. In pregnancy the demand for thyroxine is increased, and it is well established that goiters may appear or enlarge during gestation<sup>10</sup> in areas of low environmental iodine. With the increased thyroid function in pregnancy, a low availability of iodine places a double stress on the thyroid. If this is too great for its compensating capacity, hypothyroidism may result.

Hyperthyroid states are reported to produce a lowering of the serum cholesterol level while hypothyroid states lead to an increase, occasionally quite marked.<sup>11</sup> Nevertheless, Peters and Man<sup>12</sup> concluded that serum cholesterol determinations are not consistently useful in the detection of overactivity of the thyroid gland. The present data provide no evidence to suggest that the quantitatively greater elevation of serum cholesterol levels observed in lower economic as compared to upper economic Guatemalan women may be attributed to a relatively lower thyroid function during pregnancy in the former group. In spite of the marked differences in dietary habits and socioeconomic status, the PBI values for both groups were within normal limits and the PBI levels of nonpregnant women of the two groups did not differ significantly. The possible exception is the positive correlation between PBI and cholesterol and between PBI and lipid phosphorus obtained at the time of delivery of the lower income women.

A substantial elevation in PBI, serum lipid concentrations, and lipid phosphorus was observed in both groups during pregnancy. The previously reported phenomenon<sup>2</sup> of the relatively greater elevation of serum cholesterol during pregnancy in women of the lower economic status was also confirmed. As repeatedly described for cholesterol in both children and adults<sup>1, 13</sup> lipid phospho-

rus levels were found to differ in nonpregnant women of the two socioeconomic groups; the higher income group had higher phosphorus and cholesterol levels. Like serum cholesterol, lipid phosphorus also rose more during pregnancy in the women of the lower socioeconomic status. On the other hand, total lipids did not differ between the two socioeconomic groups either in nonpregnant women or at delivery, although a significant rise during pregnancy was observed.

### Summary

Total lipids, cholesterol, lipid phosphorus, and protein-bound iodine (PBI) concentrations were determined in nonpregnant and pregnant women at the time of delivery in two widely different socioeconomic groups in Guatemala City. Upper income nonpregnant women had higher serum levels of lipid phosphorus and cholesterol than those of lower income, but the difference in total serum lipids and in PBI levels were not significant. All serum constituents measured increased markedly during pregnancy. At the time of delivery, no significant differences were found between the two socioeconomic groups, since quantitatively greater increases in cholesterol and lipid phosphorus occurred during pregnancy in the lower socioeconomic group. Although it had been suspected that the combined stress of pregnancy and iodine deficiency might have been producing a relative thyroid hypofunction in the lower income women, which was in turn responsible for the relatively greater increase of serum cholesterol and lipid phosphorus during pregnancy in this group, the PBI data did not support this hypothesis.

We are grateful to the Medical Staff of the Maternity Ward of the Roosevelt Hospital of Guatemala; to Drs. R. Alvarez, E. Castillo, O. Herrera, A. Jiménez Pinto, and H. Montenegro for their interest in making their patients available for this study; and to Miss Marta Rosa Díaz and Mr. Rolando Funes for technical assistance in the determination of serum lipids and protein-bound iodine.

## REFERENCES

1. Mann, G. V., Muñoz, J. A., and Scrimshaw, N. S.: *Am. J. Med.* 19: 25, 1955.
2. Méndez, J., Savits, B. S., Flores, M., and Scrimshaw, N. S.: *Am. J. Clin. Nutrition* 7: 595, 1959.
3. Abell, L. L., Levy, B. B., Brodie, B. B., and Kendall, F. E.: *J. Biol. Chem.* 195: 357, 1952.
4. Maclay, E.: *Am. J. M. Technol.* 17: 265, 1951.
5. Bragdon, J. H.: *J. Biol. Chem.* 190: 513, 1951.
6. Grossmann, A., and Grossmann, G. F.: *J. Clin. Endocrinol.* 15: 354, 1955.
7. Freedberg, I. M., Hamolsky, M. W., and Freedberg, A. S.: *New England J. Med.* 256: 551, 1957.
8. Stoffer, R. P., Koeneke, I. A., Chesky, V. E., and Hellwig, C. A.: *AM. J. OBST. & GYNEC.* 74: 300, 1957.
9. Freedberg, I. M., Hamolsky, N. W., and Freedberg, A. S.: *New England J. Med.* 256: 505, 1957.
10. Crile, G.: *Practical Aspects of Thyroid Disease*, Philadelphia and London, 1949, W. B. Saunders Company.
11. Gerlter, M. M., and White, P. D.: *Coronary Heart Disease in Young Adults*, Cambridge, Massachusetts, 1954, Harvard University Press.
12. Peters, J. P., and Man, E. B.: *J. Clin. Invest.* 29: 1, 1950.
13. Scrimshaw, N. S., Balsam, A., and Arroyave, G.: *Am. J. Clin. Nutrition* 5: 629, 1957.



# Direct measurement of milk ejection pressure in unanesthetized lactating humans

EMANUEL A. FRIEDMAN, M.D.

New York, New York

MAMMARY myoepithelial responses to intrinsic and exogenous stimuli have heretofore been studied only in lower mammals. The latter methods of study have, reached a state of development worthy of note, principally through the efforts of Cross and van Dyke,<sup>5</sup> van Dyke and associates,<sup>11</sup> and Berde and Cerletti.<sup>1</sup> A modification of the van Dyke method has been adapted to the study of milk ejection in lactating women. To our knowledge there have been no, previously published accounts of similar results involving human subjects.

Extensive reviews of the general physiology of lactation and associated clinical studies are available,<sup>6, 8, 9, 11</sup> obviating the need for repetition here. Suffice it to say that the field is far from completely clarified despite the great strides being made in the basic disciplines. The necessity for objective and quantitatively accurate observations in humans is apparent.

## Methods and materials

The van Dyke technique for measuring milk ejection pressure in the cannulated mammary ducts of anesthetized rabbits was modified for use in unanesthetized

women. Pressures were picked up externally at the nipple of the lactating breast by means of a newly designed open-end polystyrene adapter (Fig. 1). This was applied directly to the breast with inner petrolatum seal and held securely by slight negative pressure created by gentle evacuation of the outer chamber. The inner chamber, containing 0.9 per cent saline, was connected by means of a three-way stopcock (for fill-

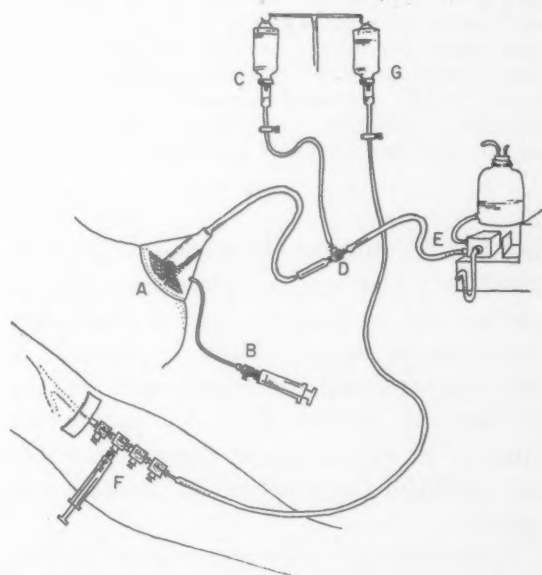


Fig. 1. Diagrammatic representation of technique employed. Polystyrene adapter A with inner chamber connected via stopcock D to flushing system C and electromanometer E and recorder (not shown); outer chamber of adapter evacuated gently for purchase via tubing and syringe B. Tandem stopcock arrangement F for uncontaminated administration of test drugs, through which flows constant infusion of saline G.

*From the Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, and the Sloane Hospital for Women, Columbia-Presbyterian Medical Center.*

*This work was supported by a grant-in-aid from the Sandoz Pharmaceuticals Division of Sandoz, Inc., Hanover, New Jersey.*

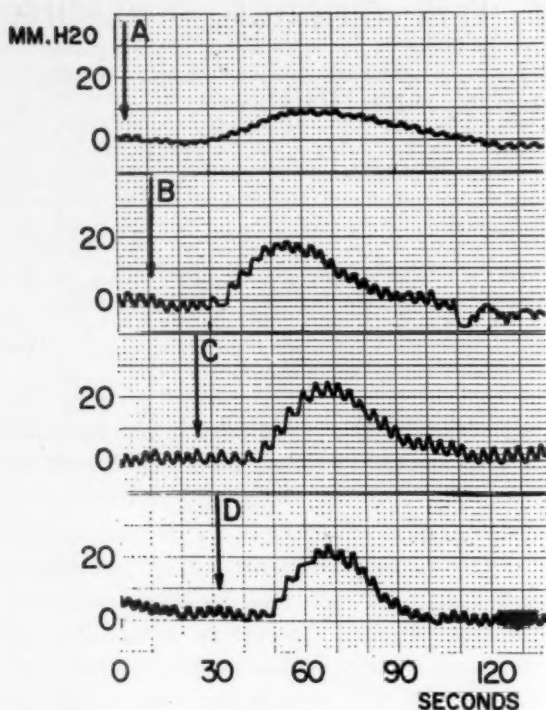


Fig. 2. Examples of milk ejection responses to ejector principles administered in minute intravenous dosages. The horizontal scale is 2 seconds per millimeter; the vertical scale 2 mm. water per millimeter. At point A synthetic oxytocin 2.0 mU. was given; B synthetic oxytocin 4.0 mU.; C synthetic oxytocin 6.0 mU.; D valyl analogue of oxytocin 1.0 mU. Increased responsiveness to increasing dose is apparent. The greater relative potency of the valyl preparation is noteworthy.

ing and for flushing the system of air bubbles) to a high sensitivity condenser-microphone of a Sanborn electromanometer capacitance bridge. Minute changes in pressure reaching the diaphragm of the microphone via the fluid system produce changes in the output of the bridge which are amplified and recorded on precalibrated paper.

The subjects studied were all volunteers, recently delivered and freshly lactating; many were private obstetrical patients of the author. No discomfort was involved in the application of the equipment to the breast. There were no ill effects noted at any time during the various studies. No form of anesthesia or sedation was used nor was it ever deemed necessary.

Drugs evaluated for this preliminary report were all administered intravenously so as to add to the extreme sensitivity of the method. The preparations used included natural oxytocin (Pitocin), synthetic oxytocin (Syntocinon), and phenylalanyl and valyl analogues of oxytocin (in which the isoleucyl group of the oxytocin molecule is replaced by phenylalanyl and valyl groups, respectively.\*) Multiple dosages were employed in efforts to obtain dose-response curves; 3 minute intervals between administrations were adhered to throughout. Drugs were given by means of 4 three-way stopcocks in tandem (one for each drug so as to prevent cross-contamination between the various preparations) through which flowed a continuous saline infusion. Standard assay techniques of administration were ultimately employed (four-point assay<sup>7, 10</sup>) after preliminary trials to determine the dosage ranges required.

### Results

The wave pattern of the milk ejection pressure produced by myoepithelial contraction follows the administration of an ejector principle after a latent period which averages 20 seconds; the wave lasts between 40 and 60 seconds. The amplitude of response depends on the intensity of the stimulus (Fig. 2), maximum being around 30 mm. of water. The wave itself appears to be asymmetrical in that the upstroke is more steeply inclined than the gradually descending downstroke.

Rare large spontaneous myoepithelial contractions are seen, apparently mediated through psychic stimuli, as for example upon the approach of the hungry infant or, on several occasions, of the patient's husband. These contraction patterns are longer in duration and greater in amplitude than those produced by our drug administrations. They are followed by prolonged refractory periods of up to 10 minutes during which time milk ejection responses to medi-

\*These were synthesized by Boissonnas and associates<sup>4</sup> and made available to us through their generosity.

Table I. Milk ejection response data

Drug	Dose (mU.)	Range of response (mm. H <sub>2</sub> O)
Oxytocin, synthetic (Syntocinon)	2.5	6-11
	5.0	17-22
	10.0	24-29
Oxytocin, natural (Pitocin)	2.5	5-11
	5.0	16-22
	10.0	25-30
Phenylalanyl analogue	1.0	3-9
	2.0	12-17
	4.0	23-27
Valyl analogue	0.5	5-10
	1.0	16-21
	2.0	24-29

cation are minimal and inconstant. This is not considered to constitute a major drawback to the method, nor to warrant the use of anesthesia since these episodes occur only quite rarely.

Fig. 3 summarizes data for the approximate dose-response curves obtained (eye-fit) for the several preparations evaluated.

These data are tabulated in Table I, which gives the range of responses in millimeters of water pressure as seen following varying doses of the several drugs in a total of 96 such administrations.

It is clear that synthetic and natural oxytocins are equivalent in so far as milk ejection qualities are concerned; the phenylalanyl analogue of oxytocin possesses about twice the milk ejection potency; the valyl analogue possesses still more (about 5 times that of oxytocin). If one studies these curves, one determines a relative equivalent effect with reference to milk ejection of the order of 10 units oxytocin to 5 units phenylalanyl derivative to 2 units valyl derivative. This was confirmed by bioassay techniques and verifies the results obtained in animal experiments.<sup>2, 3</sup>

Minimum amounts of preparation necessary to elicit detectable responses are of the order of 1.0 mU. oxytocin, 0.5 mU. phenylalanyl analogue and 0.2 mU. valyl analogue. Assuming crystalline oxytocin to have the equivalent of 500 uterotonic units per milli-

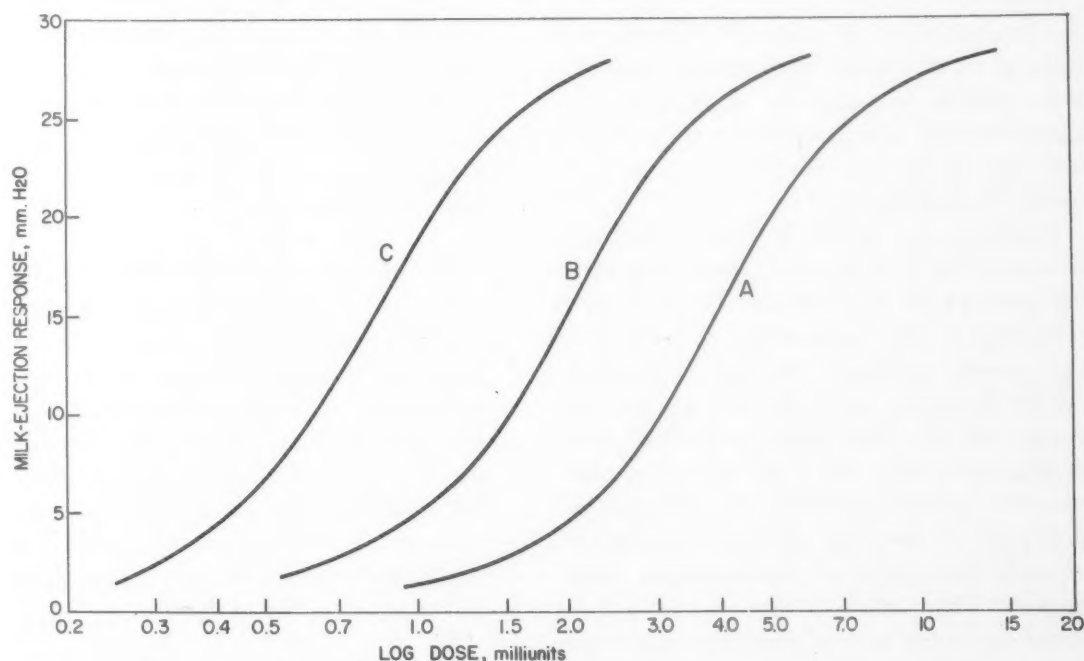


Fig. 3. Dose-response curves estimated from milk ejection data obtained from unanesthetized lactating women. The curve A represents that obtained with both synthetic and natural oxytocin; B the curve of the phenylalanyl analogue; C valyl analogue. The ratio of effectiveness is 10 units oxytocin to 5 units phenylalanyl derivative to 2 units of valyl derivative.



gram, one may quickly derive the figure of 0.000002 mg. (2  $\mu$ g), which corresponds to 1.0 mU., as the amount of crystalline oxytocin which will stimulate the myoepithelial cells sufficiently to produce the aforementioned detectable ejection response. These quantities correspond closely to probable physiologic levels.

The preparations tested, although not all solutions of purified crystalline substances, were subjected to standard animal assays (performed by Sandoz, Inc.) which yielded data on the existence of variable oxytocic, antidiuretic, and pressor effects. For example, the stock dilution of the phenylalanyl derivative (equivalent of 10 I.U. oxytocin), when tested against international posterior pituitary powder, had a potency of 1 I.U. per cubic centimeter pressor effect in spinal cats, and 6 I.U. per cubic centimeter antidiuretic effect in rats; the valyl preparation possessed 2 I.U. per cubic centimeter of rat uterus oxytocic activity and blood pressure effect as measured in chickens.

#### Comment

The specificity of action of oxytocin and some of its analogues on human myoepithelium during lactation is implied in this study. Indeed, it would appear to be clearly indicated by the extreme sensitivity of demonstrated responses.

Complete specificity is neither assumed nor expected, it being well known that varying proportions of cross-reaction exist with reference to the various known actions of the several members of the octapeptide amide hormone complex. The current investigation does not delve into these cross actions and does not seek potential milk ejection moieties present in the various preparations because of the concurrence of such principles as, for example, vasopressin. The latter is known to possess about one fifth to one sixth the milk ejection potency of oxytocin, and therefore suitable corrections for its presence should be made in bioassays, as recommended by van Dyke and co-workers.<sup>11</sup>

Our interest to date, however, is not so much in the field of bioassay as in the objective demonstration of physiological mechanisms in the human. It is to this end that our efforts are being directed. The pitfalls of utilizing data obtained solely from animal experimentation for interpretation of physiological phenomena in man are paramount. These may be avoided only through adequate observations of normal human material, the *raison d'être* of studies such as this.

The neurohumoral milk ejection reflex, variously called the "let-down" or "draught" reflex, appears to be mediated by way of afferent stimuli from nerve endings in the nipple and areola to the hypothalamic-neurohypophyseal system with resulting liberation of the effective hormonal principle. The elucidation of the latter principle and the end-organ response in the prepared breast concerns us here. A method of in vivo study has been evolved for this purpose, allowing for the evaluation of several natural and synthesized preparations, of the potential relationships between activity and chemical structure, and of the reflex responsiveness in various states of health and disease. The latter is a clinical field sorely in need of illumination from the points of view of both milk production and suppression of lactation in both human and veterinarian populations.

#### Conclusions and summary

A method is presented for measuring the effective milk ejection pressure in vivo of lactating humans without the necessity of anesthesia or surgical cannulation of the mammary ducts (ductus lactiferus). This preliminary report delves superficially into the relative effectiveness in eliciting milk ejection of several natural and synthetic hormone preparations, as measured by this extremely sensitive technique.

---

#### REFERENCES

1. Berde, B., and Cerletti, A.: *Gynaecologia* **144**: 275, 1957.



2. Berde, B., Doepner, W., and Konzett, H.: Brit. J. Pharmacol. 12: 209, 1957.
3. Boissonnas, R. A., et al.: Nature 178: 260, 1956.
4. Boissonnas, R. A., et al.: Helvet. chim. acta 39: 1421, 1956.
5. Cross, B. A., and van Dyke, H. B.: J. Endocrinol. 9: 232, 1953.
6. Douglas, R. G., Kramer, E. E., and Bonsnes, R. W.: AM. J. OBST. & GYNEC. 73: 1206, 1957.
7. Finney, D. J.: Statistical Method in Biological Assay, New York, 1952, Hafner Publishing Company.
8. Newton, M., and Newton, N. R.: J. Pediat. 33: 698, 1948.
9. Nickerson, K., et al.: AM. J. OBST. & GYNEC. 67: 1028, 1954.
10. Schild, H. O.: J. Physiol. 101: 115, 1942.
11. van Dyke, H. B., Adamsons, K., Jr., and Engel, S. L.: In Pincus, Gregory: Recent Progress Hormone Research, New York, 1955, Academic Press, Inc., Vol. 11, p. 1.

# Lactation with a phenothiazine derivative (Temaril)

## A case report

HARRY W. JOHNSON, M.D.  
DASNI POSHYACHINDA, M.D.  
GLENN McCORMICK, M.D.  
E. C. HAMBLIN, M.D.

*Durham, North Carolina*

RECENT years have brought new pharmacologically active compounds, termed tranquilizers. These drugs have been used commonly in most branches of medicine, particularly in psychiatry (psychoses and neuroses), dermatology (pruritus), and obstetrics (nausea and vomiting). Tranquilizers in general use today can be divided into 4 chemical groups<sup>4</sup>: (1) phenothiazine derivatives, (2) reserpine and its related alkaloids, (3) diphenylmethane derivatives, and (4) substituted propanediols, meprobamate. As with most drugs, these compounds have some side effects; one of these, namely, lactation, is of especial interest to the gynecologist, obstetrician, and endocrinologist. Lactation has been reported with drugs in the first two named groups, i.e., phenothiazine and reserpine.<sup>1, 2, 8, 12</sup>

The purpose of this report is to describe lactation in a patient receiving Temaril (3-dimethylamino-2-methylpropylphenothia-

zine). The clinical value of Temaril is primarily in the control of pruritus, and until now no reports of lactation from this drug have appeared in the literature. Such reports, however, might well be anticipated.

We will offer also a possible explanation for the mechanism of lactation produced by the phenothiazines and reserpine.

**History.** R. P., a 46-year-old white married woman, para 4-0-5, was first seen in the Dermatology Clinic, Duke Hospital, on Jan. 9, 1958, with the complaint of intermittent bullous eruption of one month's duration. Familial benign chronic pemphigus (Hailey-Hailey's disease) was diagnosed and the patient was started on Aristocort (triamcinolone), 16 mg. per day, and local dermatological applications. The dosage of Aristocort was varied from 4 to 20 mg. per day according to the severity of the disease. The patient became progressively worse and was admitted to the hospital on Aug. 18, 1958. On this admission the diagnosis was changed to pemphigus vulgaris. The steroid medication was continued, and Temaril, 50 mg. per day, was started to combat severe pruritus. She improved and was discharged on Aug. 27, 1958, to be followed in the outpatient clinic. The dosage of Temaril was reduced to 20 mg. per day.

Two weeks after Temaril therapy was started, the patient noted enlargement of her breasts, and spontaneous discharge of a milky fluid oc-

*From the Department of Obstetrics and Gynecology, Division of Endocrinology, and from the Department of Medicine, Division of Dermatology, Duke University Medical Center.*

*Part of the expenses of these studies was defrayed by grants from the Research Council of Duke University and from Ayerst Laboratories, New York, New York, to one of us (E. C. H.).*

curred one week later. She then was referred to the Division of Endocrinology for evaluation of the lactation.

General health had always been good. Pubescence had been normal; there was no history to suggest endocrinopathy. Menarche was at the age of 13 years. Periods occurred cyclically approximately once a month and lasted 4 to 6 days, requiring 4 to 5 pads per day. The last menstrual period was Sept. 17, 1958; previous menstrual period was in early August, 1958. She had had 4 normal deliveries (one set of twins). She nursed her first baby one year but did not nurse subsequent children although she lactated after each pregnancy. The last delivery occurred in 1946.

**Physical examination.** Blood pressure was 130/80, pulse 72 per minute, respirations 20 per minute. The patient was well developed and well nourished with a striking Cushingoid appearance (Aristocort therapy). There were multiple bullous lesions scattered over her trunk and limbs. The breasts were gynecoid Type IV (Stratz's classification), large and engorged without masses or tenderness. Stripping of the breasts produced a small amount of white, milky fluid. The remainder of the physical and the neurological findings were normal.

Laboratory findings included: hemoglobin 13.9 Gm. per cent, hematocrit 42 per cent, white blood count 12,759 per cubic millimeter with normal differential; sedimentation rate, corrected 14.5 mm. per hour. Urinary findings were normal. Blood chemistry showed: nonprotein nitrogen 38 mg. per cent, sodium 142 mEq. per liter, chloride 102 mEq. per liter, potassium 4.2 mEq. per liter, and fasting blood sugar 87 mg. per cent. Roentgenogram of the skull showed normal sella turcica. Visual fields were grossly normal. Urinary 17-ketosteroids were 3.3 mg. per 24 hours (slightly low) and 17-hydroxycorticoids were 0.9 mg. per 24 hours (low, consistent with Aristocort therapy). The secretion from the breasts was examined microscopically and was found to contain fat globules.

**Follow-up.** The patient continued to take Temaril, 20 mg. per day, and was cautioned against breast manipulation. The secretion no longer occurred spontaneously but could be expressed when she was seen on Oct. 28, 1958, although she had stopped Temaril on Oct. 21, 1958, of her own volition. The breasts remained enlarged and engorged.

### Comment

Nonpuerperal lactation, as in our patient, has been reported under many diverse conditions, including pituitary or juxtapituitary tumors, of iatrogenic etiology, and of idiopathic cause. There are many reports of lactation in patients with pituitary or juxtapituitary tumors.<sup>7, 13</sup> Normal appearing sella turcica, normal visual fields, and absence of neurological signs associated with cyclic periods in our patient discounted a diagnosis of pituitary or juxtapituitary tumor. However, since our patient received Aristocort and Temaril, the iatrogenic etiology has to be considered. Jones and associates<sup>9</sup> reported a patient with "idiopathic amenorrhea" who developed galactorrhea after cessation of cortisone therapy. It seems improbable that the cortisone derivative, Aristocort, produced galactorrhea in our patient because she was still receiving Aristocort when the galactorrhea developed. The remaining probable cause was therapy with Temaril, a phenothiazine derivative, and, in view of many reports of lactation produced by this chemical group,<sup>8</sup> we concluded that the lactation in this patient was caused by Temaril.

Many reports of lactation with chlorpromazine are recorded in the literature.<sup>1, 2, 12</sup> Ayd,<sup>1</sup> in 1955, reported as great as an 80 per cent incidence of lactation in psychotic patients treated with chlorpromazine, and, in his subsequent article<sup>2</sup> in 1956, he reported only one patient lactating in a group of 84 psychotic patients receiving chlorpromazine, 100 to 150 mg. per day. Robinson<sup>12</sup> reported 70 patients (41 premenopausal and 29 postmenopausal) who were treated with chlorpromazine for over one month with 7 (10 per cent) lactating. These lactating patients were in the premenopausal group, giving an incidence of 17 per cent in this age group. The 7 patients who lactated were on large doses of chlorpromazine. Robinson also reported 2 patients on reserpine therapy who had lactation, and one elderly man who developed gynecomastia. In both instances, i.e., with both chlorpromazine and reserpine, the lac-

tation and breast engorgement improved following cessation of therapy. Most of the patients reported were psychotic, and we cannot rule out a psychogenic cause for the lactation, as reported by Foss and Short.<sup>7</sup> Cessation of lactation following elimination of therapy would, however, seem to discount the psychosis as a cause.

The action of phenothiazine derivatives and reserpine is thought to be as "autonomic suppressants."<sup>4</sup> Barraclough and Sawyer<sup>3</sup> showed in their experiments with the EEG in rats that chlorpromazine increases the threshold stimulation of the mid-brain reticular formation. The same authors showed reserpine increases the threshold stimulation, not in the reticular formation but in cerebellum and lateral nuclei. These studies suggest the site of action of these drugs is primarily the diencephalon. These authors also showed that LH (luteinizing gonadotropic hormone) and, hence, ovulation could be blocked by both chlorpromazine and reserpine if the sedation by these drugs is accomplished prior to ovulation. These actions and EEG changes are similar to those produced by atropine, Nembutal, and morphine.<sup>3, 4</sup>

Meites<sup>10</sup> has produced lactation with reserpine in estrogen-primed rabbits. He also determined a rise in prolactin in these lactating rabbits. How these drugs cause lactation has not been ascertained. It has been suggested that at least reserpine may act directly on the mammary tissue.<sup>5</sup>

In all case reports, including ours, the women who developed lactation with these drugs were in the reproductive age group. It would therefore appear necessary for the breast tissue to be prepared by estrogens as was the case in Meites's rabbits. During pregnancy the breasts are prepared for lactation by estrogen and progesterone. Estro-

gen alone causes development of the breast ducts and in proper levels will activate the lactogenic function of the anterior pituitary. Throughout pregnancy the levels of progesterone inhibit the lactogenic effect of estrogen.<sup>6</sup> Folley<sup>6</sup> states "the relative fall in the ratio of progesterone to estrogen at parturition . . . removes the inhibition which is replaced by the positive lactogenic effect of estrogen being unopposed." Polishuk and Kulscar<sup>11</sup> have shown that patients receiving chlorpromazine have normal or elevated urinary FSH (follicle-stimulating gonadotropic hormone) coexistent with amenorrhea. This finding is in accord with Barraclough and Sawyer's report<sup>3</sup> of blockage of LH secretion from anterior pituitary in spontaneously ovulating animals.

The hypothesis we propose is a selected suppression of LH release associated with a selective stimulation of prolactin secretion by the anterior pituitary following blockage of neurological stimuli of the higher centers. These changes in secretion of LH and prolactin are independent of normal or elevated levels of FSH. Blockage of LH secretion would markedly decrease the level of progesterone. The fall of progesterone associated with normal estrogen and elevated prolactin would fulfill the requirement for the initiation of lactation as proposed by Folley.<sup>6</sup>

### Summary

1. A case of lactation during treatment with Temaril is presented.
2. A possible mechanism of action in the production of lactation by phenothiazine derivatives and reserpine is discussed.
3. The exact mechanism of action of these drugs in producing lactation is unknown, and further work is needed before the problem is elucidated.

### REFERENCES

1. Ayd, F. J., Jr.: Chlorpromazine and Mental Health. Proceedings of the Symposium Held Under the Auspices of Smith, Kline & French Laboratories, Philadelphia, 1955, Lea & Febiger.
2. Ayd, F. J., Jr.: Am. J. Psychiat. 113: 16, 1956.
3. Barraclough, C. A., and Sawyer, C. H.: Endocrinology 61: 341, 1957.
4. Berger, F. M.: Ann. New York Acad. Sc. 67: 675, 1957.



5. Durlach, J.: Presse méd. 65: 2060, 1957.
6. Folley, S. J.: The Physiology and Biochemistry of Lactation, Springfield, Ill., 1957, Charles C Thomas, Publisher.
7. Foss, G. L., and Short, D.: J. Obst. & Gynaec. Brit. Emp. 58: 35, 1951.
8. Hamblen, E. C., and Del Corral, F.: Rev. colomb. obstet. y ginec. 10: 45, 1959.
9. Jones, G. E. S., Howard, J. E., and Langford, H.: Fertil. & Steril. 4: 49, 1953.
10. Meites, J.: Proc. Soc. Exper. Biol. & Med. 96: 728, 1957.
11. Polishuk, W. C., and Kulscar, S.: J. Clin. Endocrinol. 16: 292, 1956.
12. Robinson, B.: M. J. Australia 2: 239, 1957.
13. Toaff, R., and Sadovsky, A.: Harefuah 41: 189, 1951.

# A comparative controlled study of hormones used in the prevention of postpartum breast engorgement and lactation

KARL E. MARKIN, M.D.\*

MACK D. WOLST, JR., M.D.

*Rochester, New York*

APPROXIMATELY 75 per cent of the women who are delivered in our hospital at the present time choose not to nurse their infants. A frequent consequence of this failure to nurse is the development of painful breast engorgement and lactation beginning on the third or fourth postpartum day and lasting for 48 to 72 hours. Although the pain, engorgement, and lactation do not of themselves result in any serious or permanent harm, the prevention or amelioration of these manifestations is desirable in order to give the nonnursing mother a maximum of comfort during the postpartum period. However, any medications employed for this purpose must not create new problems. Preparations which merely postpone the postpartum manifestations or which induce other unwanted responses (such as withdrawal bleeding) are not desirable therapeutic agents to employ in our efforts to control these physiologic processes. The uncomfortable manifestations are treated most easily in the hospital, and not after the patient has gone home. Finally, since these processes, or the reactions to them, are largely subjective, the patients' evaluation of the prevention or treatment of

the symptoms should bear considerable weight in the final evaluation of any preparation used.

Since 1933, when Smith and Smith<sup>19</sup> demonstrated that estrogen inhibited postpartum lactation in rabbits, there has developed a plethora of literature concerning dozens of endocrine preparations, alone and in combination, purported to relieve the nonnursing mother of breast engorgement.<sup>1-18, 20-22</sup> The results reported with the use of these various preparations often have been contradictory and poorly controlled and usually have not been analyzed statistically. Furthermore, in clinical practice we have not been able consistently to reproduce the good results that have been reported to follow the use of these various agents. Therefore, we have undertaken on our own patients an evaluation of the relative efficacy of 5 commonly used endocrine preparations by conducting a double-blind placebo-controlled study in which the results have been subjected to statistical analysis.

## Experimental procedures

**A. Patients and general plan of study.** All of the patients who were delivered at the 4050th USAF Hospital between Jan. 11, 1957, and Sept. 12, 1958, were asked whether or not they wished to breast- or to bottle-feed; no persuasion or coercion was employed. There were 680 who elected not

*From the Obstetric Service of the 4050th USAF Hospital, Westover AFB, Massachusetts.*

*\*Present address: 140 Alaimo Drive, Rochester, New York.*

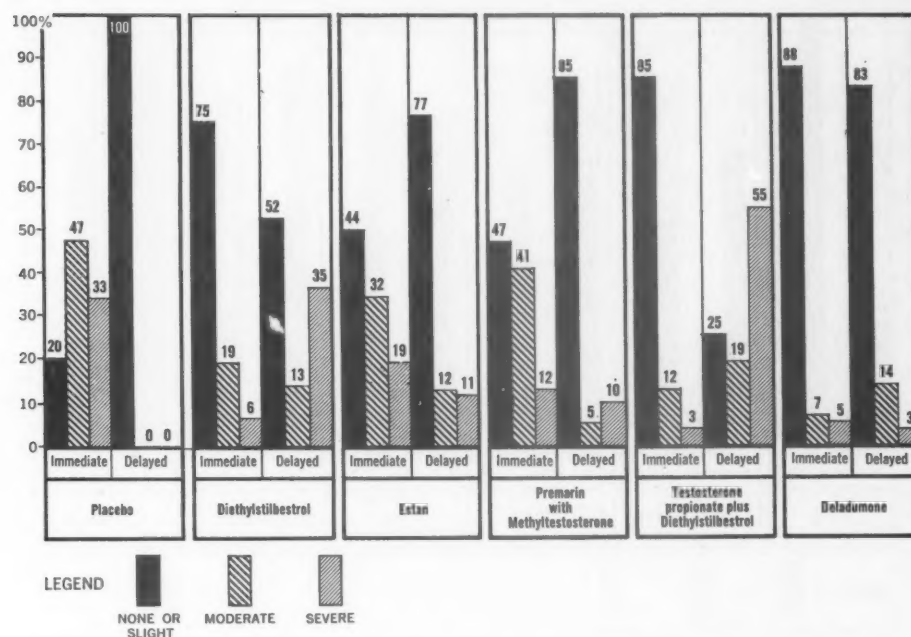


Fig. 1. Percentages of patients exhibiting postpartum breast engorgement.

to nurse their infants. One of the medications under evaluation in this study was administered as described below to each of these individuals. Upon discharge from the hospital, each patient was given the questionnaire described below and instructed to present the completed form upon return to the hospital for a postpartum visit 6 weeks after delivery. Of the 680 nonnursing patients who received one of the medications, 486 (72 per cent) returned the completed questionnaire and were examined at the postpartum visit. This communication is concerned with the results obtained in these 486 patients.

**B. Medications.** The endocrine preparations included in this study were selected because they were readily available and commonly used, and because they had been reported to be effective by other investigators.<sup>1, 5, 9, 10, 11, 15, 16, 21, 22</sup> The dosages employed were determined on the basis of the recommendation of the manufacturer or of that used in recently published reports. For each of 4 of the 5 endocrine formulations, a placebo preparation of identical appearance was administered in the same dosage to a group of patients as a control medication.

Each active or placebo preparation was labeled as either "Drug E" or "Drug O" and was administered by the nursing staff to the patients delivering on the even-numbered or the odd-numbered days of the month, respectively. The identity of the individual preparations was not known to the patients, the nurses, or the doctors.

The following materials and dosage regimens were employed:

1. *Diethylstilbestrol.* A tablet containing 5 mg. of diethylstilbestrol was administered three times a day for 5 days to 52 patients who were delivered on the odd-numbered days of the month. Forty patients who were delivered on even-numbered days received identical-appearing placebos in the same dosage.

2. *Dienestrol plus methyltestosterone.\** A tablet containing 0.25 mg. of dienestrol and 5 mg. of methyltestosterone was administered in a dosage of 3 tablets three times a day for 2 days, then 2 tablets three times a day for 2 days, and then 1 tablet three times a day for 1 day to 58 patients who were delivered on the even-numbered days of the

\*Supplied as Estan by White Laboratories, Inc., Kenilworth, New Jersey.

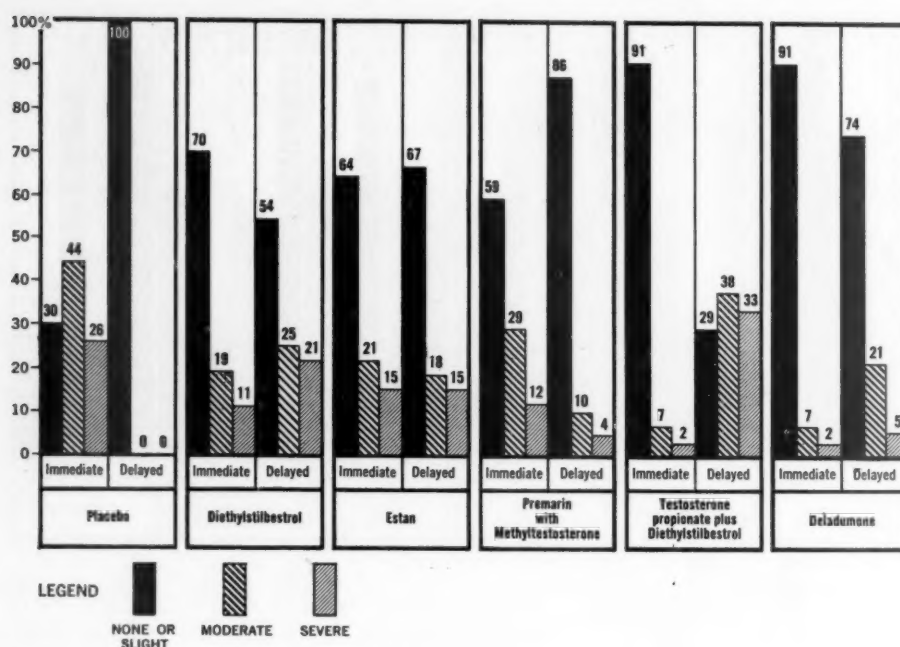


Fig. 2. Percentages of patients exhibiting postpartum lactation.

month. Seventy-two patients who were delivered on odd-numbered days received identical-appearing placebos in the same dosage.

3. *Conjugated estrogens, equine, plus methyltestosterone.\** A tablet containing 1.25 mg. of conjugated estrogens equine and 10 mg. of methyltestosterone was administered in a dosage of 2 tablets three times a day, then 2 tablets two times a day, then 1 tablet two times a day, and then 1 tablet daily for 5 days to 49 patients who were delivered on the even-numbered days of the month. Sixty-five patients who were delivered on odd-numbered days received identical-appearing placebos in the same dosage.

4. *Testosterone propionate plus diethylstilbestrol.* A single injection of 50 mg. of testosterone propionate in oil was injected intramuscularly at the time of delivery and repeated 24 hours later, and in addition a tablet containing 5 mg. of diethylstilbestrol was administered three times a day for 3 days to all 67 patients who were delivered on the odd-numbered and the even-numbered days of the month during the period of eval-

uation. This was the only group in which placebos were not used, since a parenteral placebo identical in appearance to the testosterone propionate was not available.

5. *Testosterone enanthate plus estradiol valerate.\** A parenteral preparation containing 90 mg. of testosterone enanthate and 4 mg. of estradiol valerate per cubic centimeter in oil was administered as a single injection of 4 c.c. intramuscularly at the time of delivery to 42 patients who were delivered on the odd-numbered days of the month. Forty-one patients who were delivered on even-numbered days received 4 c.c. of an identical-appearing placebo.

All of the oral preparations were started within a few hours following delivery. This was easily accomplished since the patients, with very few exceptions, were delivered under either pudendal block or saddle block anesthesia. The parenteral preparations were administered while the patient was still in the delivery room. Only one course of medication was used; no repeat courses were given.

\*Supplied as Premarin with methyltestosterone by Ayerst Laboratories, New York, New York.

\*Supplied as Deladumone by E. R. Squibb & Sons, New York, New York.



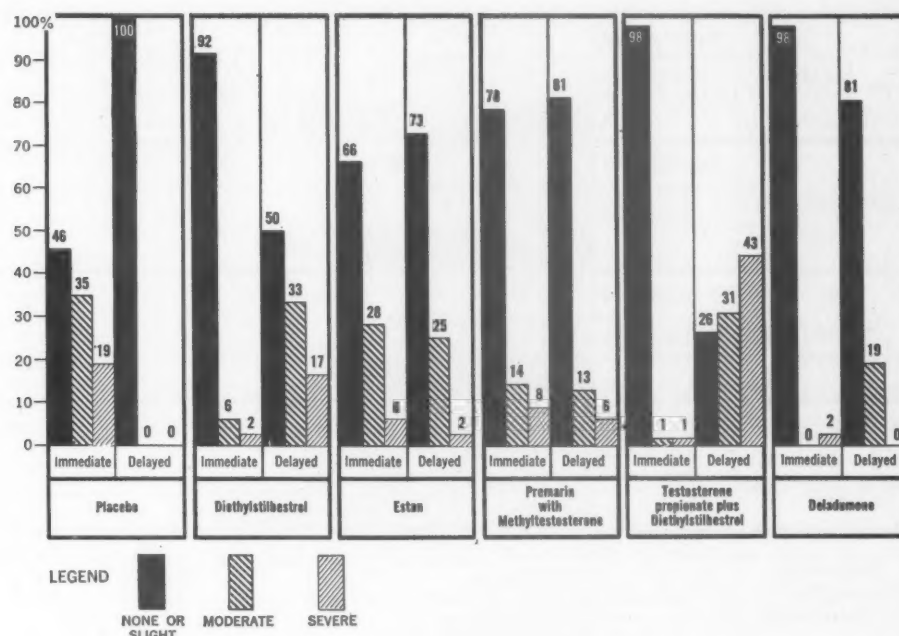


Fig. 3. Percentages of patients exhibiting postpartum breast pain.

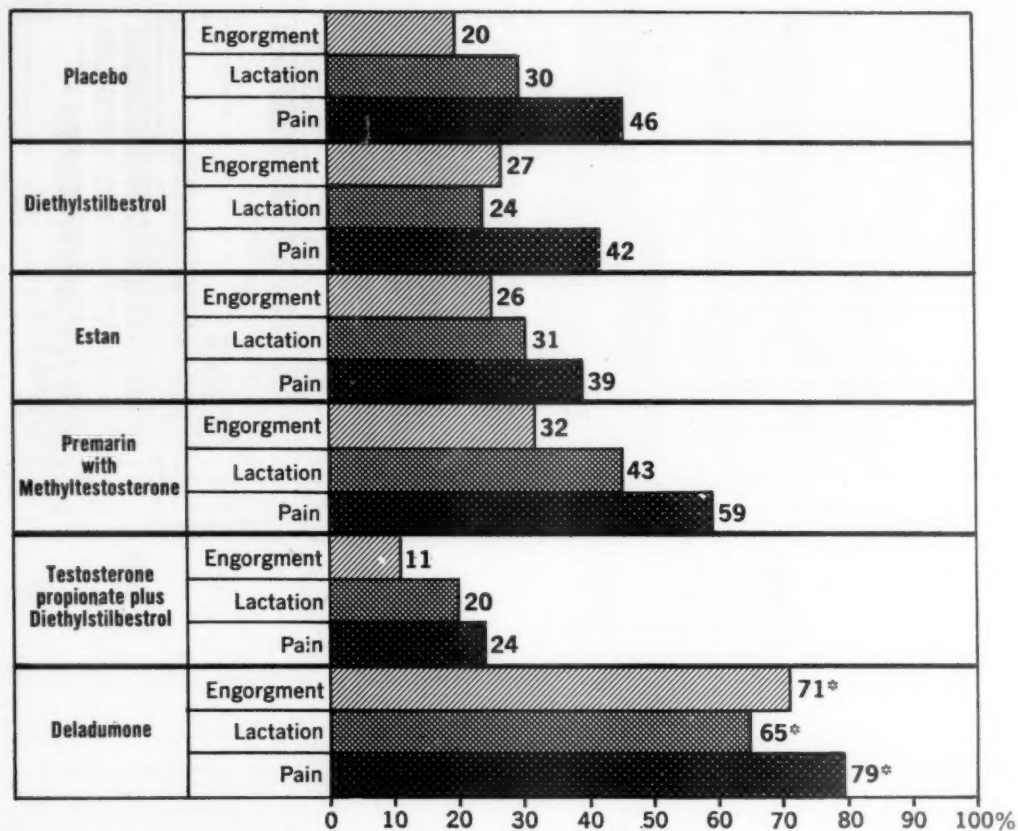
**C. General management during hospitalization.** All of the antenatal care, the deliveries, and the postpartum care were under the direct supervision of the investigators. As far as possible, the management of the patients was standardized so that the only variable was the medication that was being studied. All of the patients wore a snug (not tight) breast binder during the postpartum period. Fluids were not restricted. Aspirin, codeine, and ice bags were used as necessary. With very few exceptions, the patients were discharged to their homes on the fifth postpartum day.

**D. Patient's evaluation of result in questionnaire.** Upon discharge from the hospital, each of the patients was given a simple multiple-choice type of questionnaire. The importance of completing and returning the questionnaire at the time of the 6 weeks postpartum visit was carefully explained to each individual. It was emphasized that various types of medication were being tested and that each patient's cooperation in the study would be of general benefit to the women who would be delivered in the hospital in the future. The fact that some patients had received placebos was not disclosed.

The questionnaire was designed to determine the following information: (1) the degree, the duration, and the time of onset of breast engorgement, of lactation, and of breast pain; (2) the amount and the duration of the lochia rubra; (3) the presence or the absence of withdrawal type bleeding; (4) the time of onset of the menses (up to 6 weeks post partum); and (5) the patient's evaluation of the efficacy of the medication.

**E. Criteria for analyzing the results.** The results obtained with the various regimens of therapy were analyzed by combining the recorded observations of the authors during the period of hospitalization with the information supplied by the patients in the questionnaire. Standardized procedures were adopted for classifying the various manifestations.

The evaluation of the time of occurrence of the pain, the engorgement, and the lactation was standardized as follows: *immediate* refers to those manifestations which occurred within 3 or 4 days of the time of delivery and *delayed* refers to those manifestations which started after discharge from the hospital. Without exception, the delayed symp-



\*p less than 0.001 by the Chi-squared test

Fig. 4. "Net effectiveness" of the hormones in the suppression of postpartum breast engorgement, lactation, and pain.

toms started from 4 to 10 days after discontinuation of the oral medications. In the case of testosterone enanthate plus estradiol valerate, those few patients exhibiting delayed symptoms experienced them from 7 to 14 days after discharge from the hospital. The evaluation of the severity of these manifestations was standardized as follows: *severe* refers to those conditions in which ice bags and tight binders and/or codeine were required for the relief of engorgement and/or pain lasting more than 24 hours, or in which there was a copious flow of milk for more than 48 hours; *moderate* refers to those conditions in which small amounts of analgesics or tight binders were used electively for the relief of engorgement and/or pain lasting less than 24 hours, or in which a small amount of milk was secreted for less than 48 hours; and *slight* refers to those conditions in which there was an insignificant

degree of engorgement or pain lasting for a few hours and not requiring analgesics or binders, or in which a few drops of milk were secreted for less than 24 hours. In agreement with the observations of Stewart and Pratt,<sup>20</sup> of Dunlap and Diddle,<sup>3</sup> and of Napp and associates,<sup>13</sup> the findings in this investigation indicate that engorgement and lactation are largely independent of each other and that the prevention of one does not always mean the inhibition of the other.

The *net effectiveness* of each preparation was determined by subtracting the percentages of the patients in each group who developed moderate and severe delayed manifestations from those of the patients in the same group who experienced no immediate manifestations. The "net effectiveness" of the various endocrine regimens then was compared statistically by the chi-squared test with the "net effectiveness" of the

placebo medications. The efficacy of the various hormonal regimens as judged by the patients also was evaluated statistically by the chi-squared test against the efficacy of the placebo regimens as rated by the patients. The data on the various placebo material regimens were combined for these calculations and comparisons.

### Results

**A. Number of patients given various therapeutic regimens.** A total of 680 nonnursing mothers received one of the 9 regimens of active or placebo medication. Of these women, 194 failed to supply the necessary information on their course following discharge from the hospital and, consequently, were eliminated from the analysis of the results. The data on the 486 patients (72 per cent) who returned the completed questionnaire were analyzed for the number of patients receiving each of the various active and placebo-material regimens. There were 268 who received endocrine materials, and 218 who received placebo materials. The results for the individual therapeutic regimens are shown in Table I.

**B. Effect of therapeutic regimens on breast engorgement.** The percentages of the patients who experienced none or slight, moderate, or severe breast engorgement with the various active or placebo preparations are presented graphically in Fig. 1. The highest percentages of the patients without significant immediate engorgement were attained with the regimens of testosterone enanthate plus estradiol valerate (88 per cent), of testosterone propionate plus diethylstilbestrol (85 per cent), and of diethylstilbestrol alone (75 per cent). However, the percentage of the patients with moderate to severe *delayed* engorgement following these three therapeutic regimens was only 17 per cent with testosterone enanthate plus estradiol valerate, in contrast to 48 per cent with diethylstilbestrol alone, and to 74 per cent with testosterone propionate plus diethylstilbestrol. In summary, the percentage of the patients who developed *neither immediate nor significant delayed* breast

engorgement (i.e., the "net effectiveness") was 71 per cent for testosterone enanthate plus estradiol valerate therapy compared with 11 to 32 per cent for the other four endocrine regimens (Fig. 4).

**C. Effect of therapeutic regimens on lactation.** The percentages of the patients who experienced none or slight, moderate, or severe lactation with the various active or placebo preparations are presented graphically in Fig. 2. The highest percentages of the patients without significant *immediate* lactation were attained with the regimens of testosterone enanthate plus estradiol valerate (91 per cent), of testosterone propionate plus diethylstilbestrol (91 per cent), and of diethylstilbestrol alone (70 per cent). However, the percentage of the patients with moderate to severe *delayed* lactation following these three regimens was only 26 per cent with testosterone enanthate plus estradiol valerate, in contrast to 46 per cent with diethylstilbestrol alone, and to 71 per cent with testosterone propionate plus diethylstilbestrol. In summary, the percentage of the patients who developed *neither immediate nor significant delayed* lactation (i.e., the "net effectiveness") was 65 per cent for testosterone enanthate plus estradiol valerate therapy compared with 20 to 45 per cent for the other four endocrine regimens (Fig. 4).

**D. Effect of therapeutic regimens on breast pain.** The percentages of the patients who experienced none or slight, moderate, or severe breast pain with the various active or placebo preparations are pre-

Table I

Therapeutic regimen	Active material	Placebo material
Diethylstilbestrol	52	40
Dienesterol plus methyltestosterone	58	72
Conjugated estrogens equine plus methyltestosterone	49	65
Testosterone propionate plus diethylstilbestrol	67	0
Testosterone enanthate plus estradiol valerate	42	41
Total	268	218



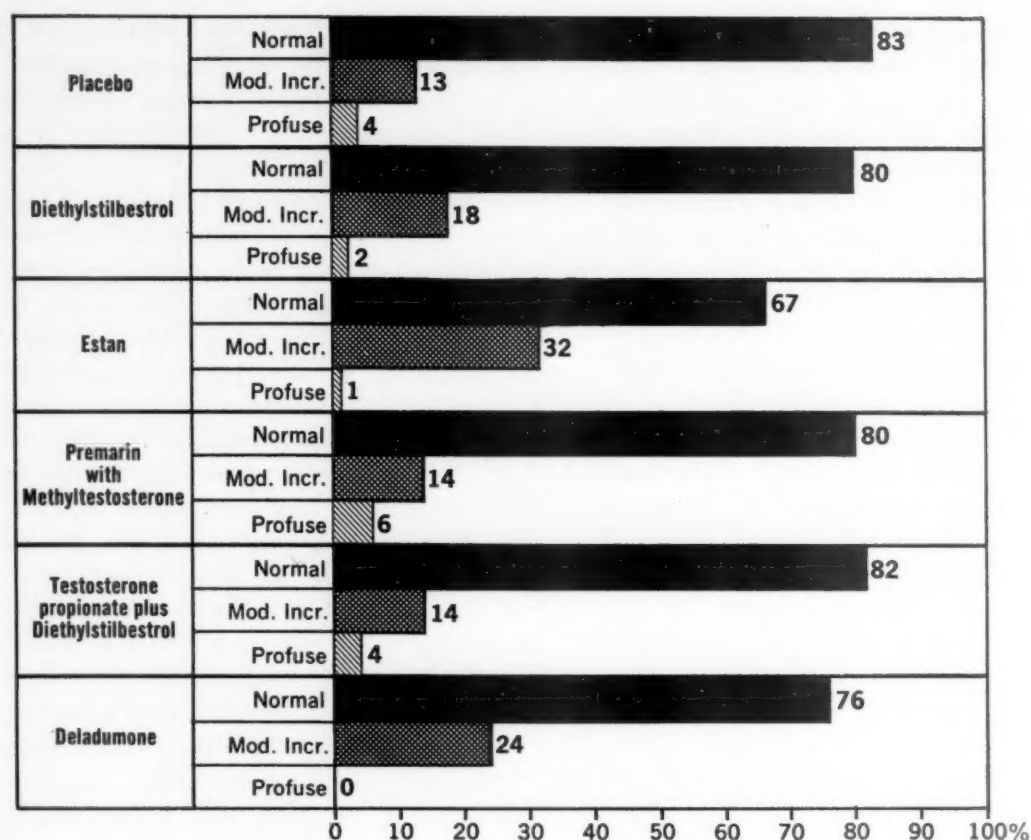


Fig. 5. Percentages of patients exhibiting normal, moderately increased, and profuse lochia rubra.

sented graphically in Fig. 3. The highest percentages of the patients without significant *immediate* pain were attained with the regimens of testosterone enanthate plus estradiol valerate (98 per cent), of testosterone propionate plus diethylstilbestrol (98 per cent), and of diethylstilbestrol alone (92 per cent). However, the percentage of the patients with moderate to severe *delayed* pain following these three regimens was only 19 per cent with testosterone enanthate plus estradiol valerate, in contrast to 50 per cent with diethylstilbestrol alone, and to 74 per cent with testosterone propionate plus diethylstilbestrol. In summary, the percentage of the patients who developed *neither immediate nor significant delayed* breast pain (i.e., the "net effectiveness") was 79 per cent for testosterone enanthate plus estradiol valerate therapy compared with 24 to 59 per cent for the other four endocrine regimens (Fig. 4).

**E. "Net effectiveness" of various endocrine regimens versus placebo regimens.** The "net effectiveness" of the various hormonal regimens compared with that of the placebo regimens on breast engorgement, lactation, and breast pain is presented graphically in Fig. 4. Testosterone enanthate plus estradiol valerate was the only endocrine preparation or regimen which gave a statistically greater net effectiveness ( $p < 0.001$  by the chi-squared test) than the placebo medications; furthermore, this medication was significantly effective in controlling all three manifestations: breast engorgement, lactation, and breast pain. Surprisingly, by this method of analysis, some of the other endocrine preparations seemed to be less effective than the placebo medications!

**F. Effect of therapeutic regimens on lochia rubra.** The percentages of the patients who reported lochia rubra which was normal, moderately increased, or profuse



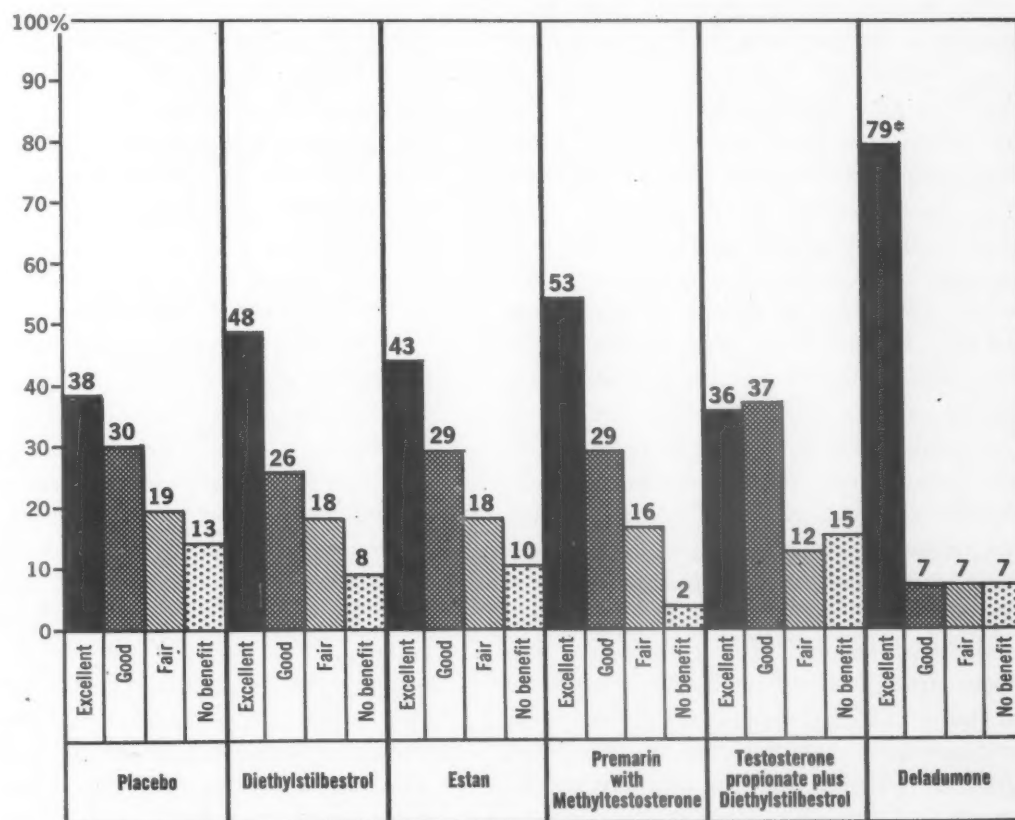
and resembling withdrawal bleeding with the various active or placebo preparations are presented graphically in Fig. 5. The amount of the lochia differed from normal in 17 per cent of the patients given placebo preparations, in 20 per cent of those given diethylstilbestrol alone, in 33 per cent of those given dienestrol plus methyltestosterone, in 20 per cent of those given conjugated estrogens equine plus methyltestosterone, in 18 per cent of those given testosterone propionate plus diethylstilbestrol, and in 24 per cent of those given testosterone enanthate plus estradiol valerate. Therefore, none of the endocrine preparations employed in this study significantly affected the lochia, and withdrawal bleeding was not a problem.

**G. Effect of therapeutic regimens on onset of menses.** Of the 218 patients in the placebo groups, 61 per cent had the onset

of their first menses following delivery after the sixth postpartum week. Each of the endocrine-treated groups had a slightly higher percentage (65 to 82 per cent) of patients in whom the menses had not appeared by the sixth postpartum week; this small increment is not significant.

**H. Other undesirable manifestations and complications.** None of the hormonal preparations employed in this study produced any apparent harmful effects. Subinvolution of the uterus, edema, and virilization were not encountered to any noticeable degree. There were two instances of breast abscess, one occurring in a patient in the placebo group and the other in a woman in the group treated with diethylstilbestrol alone. There were no other known complications.

**I. Efficacy of various endocrine regimens as rated by the patients.** The percentages of



\*p less than 0.001 by the Chi-squared test

Fig. 6. Percentages of patients rating medications as excellent, good, fair, and without benefit.

the patients who rated the various active or placebo preparations and regimens as excellent, good, fair, or without any benefit are presented graphically in Fig. 6. An "excellent" rating was given to diethylstilbestrol alone by 48 per cent, to dienestrol plus methyltestosterone by 43 per cent, to conjugated estrogen equine plus methyltestosterone by 53 per cent, to testosterone propionate plus diethylstilbestrol by 36 per cent, and to testosterone enanthate plus estradiol valerate by 79 per cent of the patients. In summary, testosterone enanthate plus estradiol valerate was the only one of the five endocrine preparations or regimens employed in this study which was outstandingly and significantly ( $p < 0.001$  by the chi-squared test) rated as better than the placebo medication by the patients themselves.

#### Comment

The physiology of lactation has been thoroughly reviewed by Roland and associates,<sup>17</sup> Rienzo,<sup>15</sup> Abarbanel and Goodfriend,<sup>1</sup> and Napp and co-workers,<sup>13</sup> and will not be considered here. All of the endocrine preparations gave moderately good results in controlling the postpartum breast manifestations while the patients were hospitalized (usually for 5 days following delivery). However, all of the agents except testosterone enanthate plus estradiol valerate failed to prevent the occurrence of delayed engorgement, lactation, and pain. Diethylstilbestrol, alone and in combination with testosterone, dienestrol plus methyltestosterone, and conjugated estrogen equine plus methyltestosterone, in the dosages used, merely succeeded in temporarily suppressing the breast symptoms. That the temporary suppression of the symptoms is not looked upon with favor by the patient is illustrated in Fig. 6, where only testosterone enanthate plus estradiol valerate was rated significantly better than the placebos by the patients.

The fallacy of attempting to evaluate the efficacy of hormonal agents in controlling postpartum breast manifestations merely

from the responses of the patients while they are in the hospital is clearly demonstrated by the data presented in Figs. 1-3. Investigations concerned with the suppression of postpartum breast engorgement and lactation must take into account the delayed symptoms produced by the temporary hormonal suppression of engorgement and lactation while the patient is receiving the medication. Our results with this phenomenon have led us to conclude that, if the suppression of postpartum breast manifestations were to be limited to the use of diethylstilbestrol alone or with testosterone, dienestrol plus methyltestosterone, or conjugated estrogen equine plus methyltestosterone, the patients would be better treated if they received no medication at all. The manifestations would then all occur while the patients were still hospitalized, where tight binders, ice bags, and analgesics can more easily be utilized.

In our experience, in contrast to the other tested endocrine preparations, testosterone enanthate plus estradiol valerate is significantly effective in the prevention of postpartum breast engorgement, lactation, and pain. We have found no complications or disadvantages attendant on the use of this preparation.

#### Summary and conclusions

1. By the use of a multiple-choice type questionnaire, 5 commonly used endocrine preparations were evaluated in a double-blind placebo-controlled study for their effectiveness in preventing postpartum breast engorgement, lactation, and pain in 680 women who did not wish to nurse their newborn infants.

2. All of the endocrine preparations evaluated gave moderately good results in controlling the postpartum breast manifestations while the patients still were in the hospital (usually for 5 days after delivery). However, all of the endocrine agents except testosterone enanthate plus estradiol valerate failed to prevent the occurrence of delayed engorgement, lactation, and pain. When the percentages of the patients de-

veloping moderate or severe delayed manifestations were subtracted from the percentages of the patients developing no immediate manifestations, the results revealed that, except for testosterone enanthate plus estradiol valerate, the endocrine preparations employed were no more effective than the placebo materials. The significance of this finding was confirmed by statistical analysis ( $p < 0.001$  by the chi-squared test).

3. None of the endocrine preparations significantly affected the lochia, and withdrawal bleeding was not a problem.

4. The onset of regular postpartum menses was delayed to a slight but not significant degree by all of the endocrine preparations.

5. None of the hormonal preparations produced harmful effects; subinvolution of

the uterus, edema, and virilization were not encountered.

6. Testosterone enanthate plus estradiol valerate was the only one of the five endocrine preparations which was rated by the treated patients as being significantly better than the placebo materials in controlling the postpartum breast manifestations. This finding was confirmed by statistical analysis ( $p < 0.001$  by the chi-squared test).

We wish to express our appreciation to Dr. Joseph A. Guthrie and Captain Mary Foster for their invaluable assistance in the conduct of this study.

We also wish to thank the following pharmaceutical houses for their generosity in supplying the preparations used in this study: White Laboratories, Inc., for Estan, Ayerst Laboratories for Premarin with Methyltestosterone, and E. R. Squibb & Sons for Deladumone.

#### REFERENCES

1. Abarbanel, A. R., and Goodfriend, M. J.: *AM. J. OBST. & GYNEC.* 40: 1037, 1940.
2. Bennet, E. T., and McCann, E. C.: *J. Maine M. A.* 45: 225, 1954.
3. Dunlap, J. C., and Diddle, A. W.: *J. Clin. Endocrinol.* 8: 880, 1948.
4. Eichner, E., Goler, G. G., Sharzer, S., and Horowitz, B.: *Obst. & Gynec.* 6: 511, 1955.
5. Fiskio, P. W.: *GP* 11: 70, 1955.
6. Garry, J.: *Obst. & Gynec.* 7: 422, 1956.
7. Hesseltine, H. C., Bustamante, J., and Navori, C. A.: *AM. J. OBST. & GYNEC.* 69: 686, 1955.
8. Katzman, B.: *AM. J. OBST. & GYNEC.* 63: 1338, 1952.
9. Laufe, L. E., and McCarthy, J. J., Jr.: *Pennsylvania M. J.* 59: 914, 1956.
10. Lo Presto, B., and Caypinar, E. Y.: *J. A. M. A.* 169: 250, 1959.
11. Mendel, E. B., Goldman, A. M., and Caire, A.: *AM. J. OBST. & GYNEC.* 42: 528, 1941.
12. Morton, D. G., and Miller, J. S.: *AM. J. OBST. & GYNEC.* 62: 1124, 1951.
13. Napp, E. E., Goldfarb, A. F., and Massell, G. M.: *West. J. Surg.* 64: 492, 1956.
14. Nulsen, R. O., Carmon, W. B., and Hendrick, H. O.: *AM. J. OBST. & GYNEC.* 65: 1048, 1953.
15. Rienzo, J. S.: *AM. J. OBST. & GYNEC.* 66: 1248, 1953.
16. Robbins, O. F., Moehn, J. T., and Mitchell, M. T.: *Minnesota Med.* 40: 794, 1957.
17. Roland, M., Veprovsky, E., and Linhart, W.: *AM. J. OBST. & GYNEC.* 70: 1004, 1955.
18. Shook, D. M.: *Am. Pract. & Digest. Treat.* 7: 917, 1956.
19. Smith, G. V., and Smith, O. W.: *Am. J. Physiol.* 103: 356, 1933.
20. Stewart, H. L., Jr., and Pratt, J. P.: *AM. J. OBST. & GYNEC.* 41: 555, 1941.
21. Watrous, J. B., Jr., Ahearn, R. E., and Carvalho, M. A.: *J. A. M. A.* 169: 246, 1959.
22. Wilson, T. M.: *M. Ann. District of Columbia* 23: 489, 1954.



# Suppression of lactation with fluoxymesterone

WESLEY W. BARE, M.D.

FRANK L. LIPPO, M.D.

Philadelphia, Pennsylvania

IN PRESENT-DAY obstetrics the suppression of lactation has become an acceptable medical procedure. This has been brought about by several factors, notably the improved methods of infant feeding with various commercial formulas and the concomitant increase in the demand of patients for "drying-up" the breasts.

Although we agree that breast feeding is still the method of choice for the newborn infant, we do not insist on this method for every woman. The decision as to method of feeding is left to the mother, but breast feeding is by no means discouraged. When a patient states her desire to bottle feed her baby, however, we believe that supportive measures are indicated to make the initial period of breast engorgement as comfortable and painless as possible.

It is not the purpose of this paper to present a comprehensive study of the intricate process of initiation of lactation in the immediate puerperium. The many excellent texts on Endocrinology do this quite well.<sup>4</sup> The onset of lactation is undoubtedly contributed to, and the continuation of lactation chiefly influenced by, the sucking reflex. Few if any of the drugs so extensively studied recently for the suppression of the initial engorgement phenomenon would succeed if the baby were regularly put to the breast. At the present time, the various methods of suppressing this painful engorgement may be divided into four main groups:

1. *Estrogens alone* may be used, by varying methods of administration. These have

been thoroughly studied on a variety of available preparations and the results have, for the most part, been quite satisfactory.<sup>3, 5</sup> The use of estrogens does have a few drawbacks, however, notably the possible occurrence of withdrawal bleeding after cessation of therapy. This usually does not occur until the patient has been discharged from the hospital and is at home with all the added responsibilities of caring for her newborn baby. In addition, it has been noted in a significant number of cases that secondary filling or lactation may occur after cessation of the estrogenic substance. A small number of patients will also become nauseated by the use of estrogens, probably as a result of direct irritation of the gastric mucosa. This is usually readily obviated by use of an enteric-coated tablet.

2. *Androgens alone* have been used to control lactation,<sup>1, 2</sup> and may be given as divided intramuscular doses of testosterone propionate or as the longer-acting, single dose form, testosterone cyclopentenylpropionate.<sup>1</sup> Androgens have the same ability as estrogens for suppression of the anterior pituitary hormones, but in addition there is some evidence to indicate that they likewise have a direct effect on the breast tissue itself to suppress the alveolar system.<sup>4</sup> They are not associated with withdrawal bleeding, but are not without local effects when given parenterally. The oral route requires larger doses than the sublingual method, which frequently leaves an objectionable taste in the patient's mouth.

3. *Combinations of estrogens and androgens* have been used with success.<sup>5</sup> The rationale behind these preparations is to ob-

*From the Department of Obstetrics and Gynecology of the Methodist Episcopal Hospital in Philadelphia.*



tain the maximum benefits of both ingredients, and to minimize the objectionable points by taking advantage of those areas in which the two ingredients are physiologically antagonistic to each other. We have always preferred not to use such preparations since they are, in the final analysis, not strictly physiologic in action.

4. Another method of controlling lactation is to use *no hormonal therapy* at all. The therapy here is merely supportive. Proponents of this method feel that all that is required is to remove the sucking reflex and the breasts automatically will "dry up" without any effort at suppression from a hormonal standpoint. Such a method makes liberal use of supportive measures such as, analgesics, breast binders, ice bags, and restriction of fluids.

The present study was undertaken to evaluate a new androgenic substance, fluoxymesterone, to determine its effectiveness for the suppression of lactation in the puerperium. This preparation is a halogenated derivative of testosterone. The molecule is 9- $\alpha$ -fluoro-11- $\beta$ -hydroxy-17- $\alpha$ -methyl-testosterone. Fig. 1 indicates the structural formula. It is a steroid with a fluorine atom replacing the hydrogen atom at the 9- $\alpha$  position and a hydroxyl group instead of the hydrogen atom in the 11- $\beta$  position. This gives properties five times that of oral methyl testosterone, and weight for weight the compound has a greater potential for therapeutic effectiveness than the injectable testosterone preparations. As an oral preparation, it eliminates painful

injections and local reactions, yet at the same time allows for smaller dosage.

#### Methods and material

This study was conducted on 193 maternity patients on the private and ward services at the Methodist Episcopal Hospital in Philadelphia. The purpose of the study was to determine both the efficacy and the optimum dosage of fluoxymesterone. The patients were divided into four groups: Group I consisted of the ward patients, who were used as the control group. There were a total of 49 patients in this group and all received only placebo tablets. Group II patients received one 5.0 mg. tablet daily; Group III patients received 5.0 mg. twice daily, and Group IV patients received 5.0 mg. three times a day. The latter three groups were all private patients, but the dosage was administered on a strict alternating basis with no attempt to select patients for a given regime. Each of these groups consisted of 48 patients.

None of the patients in any of the four groups was permitted the use of breast binders, ice bags, fluid restriction, or analgesics unless specifically ordered by the resident or attending physician, but a good supporting brassière was allowed if the patient so desired. All patients were questioned and examined daily by the attending and resident staffs, and notes were kept regarding pain in the breasts, engorgement, temperature elevation, lactation, and whether or not additional measures were required for alleviation of pain. Patients were also questioned and examined for evidence of side effects such as virilization and abnormal amounts of bleeding. Therapy was started as soon after delivery as the patient could tolerate liquids by mouth. It was continued daily until time of discharge, but not longer than the sixth postpartum day.

At the time of discharge patients were given a card with a self-addressed envelope to be returned after completion of the first menstrual period. Information requested on this card consisted of date of first menstrual period, evidence of secondary filling of the

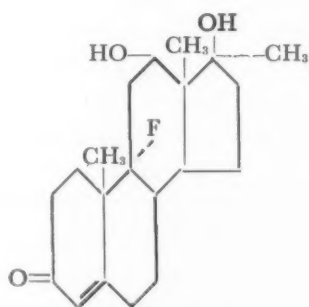


Fig. 1.

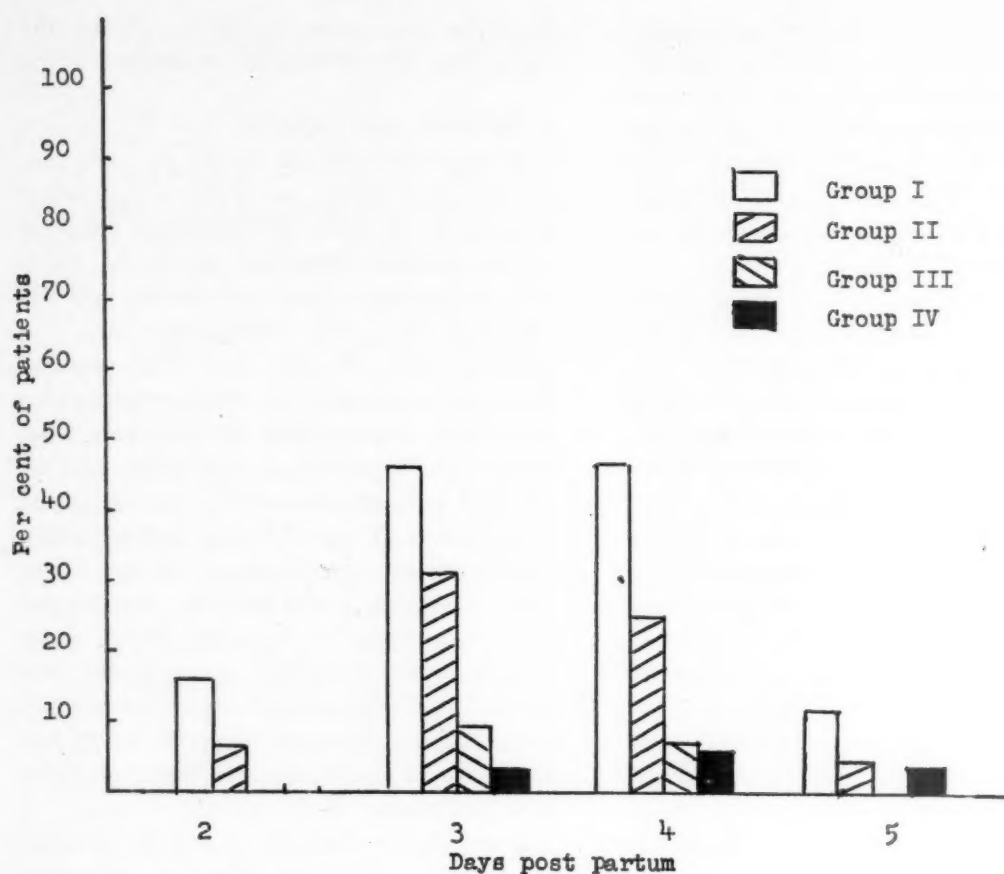


Fig. 2. Pain in the breast.

breasts, presence or absence of bleeding, and comments on any other disorders of the breast that may have arisen.

#### Results and conclusions

The number of patients in any group experiencing symptoms on the day of delivery or the first postpartum day was statistically insignificant. Likewise, no significant conclusions can be drawn after the first postpartum day, since practically all patients were symptom-free by this time. The actual evaluations, therefore, are centered on the second, third, fourth, and fifth days. Since the best criteria for success or failure of the preparation were considered to be the presence or absence of pain, engorgement, and lactation, these were taken as yardsticks by which to measure the effectiveness of the preparation.

*Pain in the breasts* was found most com-

monly in the control group receiving placebo (Fig. 2). On Days 2 and 3 this symptom was most prevalent, occurring in 47.5 per cent of all patients. Those in Group II receiving 5.0 mg. daily had less pain, but one third of these patients still complained of pain on the same 2 days. The onset of pain was at a later time, however, and was of shorter duration. In Group III, where patients received 5.0 mg. twice a day, the disappearance of pain was noticeably greater. With this dosage no patient complained of pain on Day 2, and only 9.8 per cent on Day 3, 5.8 per cent on Day 4, and none by the fifth postpartum day. Likewise, in Group IV, in patients receiving 5.0 mg. three times daily, none complained of pain on Day 2, and only 3.8 per cent complained of pain on Day 3, and 4.7 per cent on Day 4. In this group, however, 2 patients (3.84 per cent) still complained of pain on the

fifth day. Thus, with pain alone as a criterion, it would seem that the optimum dosage would be 5.0 mg. twice a day.

*Engorgement* was determined by the attending physicians by daily palpation of the breasts. Table II shows the results in the four groups with regard to this finding. It can be seen that the control group experienced filling of the breasts in about one half of the cases, rising to 52.5 per cent on the third postpartum day. Those patients in Group II likewise experienced a substantial percentage of engorgement, but here again the onset was delayed by about 24 hours in most cases. Patients in Group III likewise experienced a significant number of engorgements, rising to about one fourth of the total number by the third day. However, those encountered in this group were not as severe (as can be seen by comparison of Figs. 2 and 3), and were not associated with

pain to the degree that those of patients on lesser dosages were. The patients in Group IV had no engorgement on Day 2 and surprisingly small numbers were encountered on Day 3 (5.75 per cent) and Day 4 (7.7 per cent). Therefore, with engorgement alone as a criterion, the optimum dosage is 5.0 mg. three times a day.

*Lactation* is both a subjective and objective means of measuring the degree of success, and Table III shows the results of this finding. This complaint was not as prevalent in any group as those of a more subjective nature. Nevertheless, approximately one quarter of the patients in the control group experienced secretions from the breast, with an almost similar percentage in the Group II patients. Lactation was less evident in the Group III patients, dropping to a low of 13.6 per cent on the third postpartum day. Those patients in Group

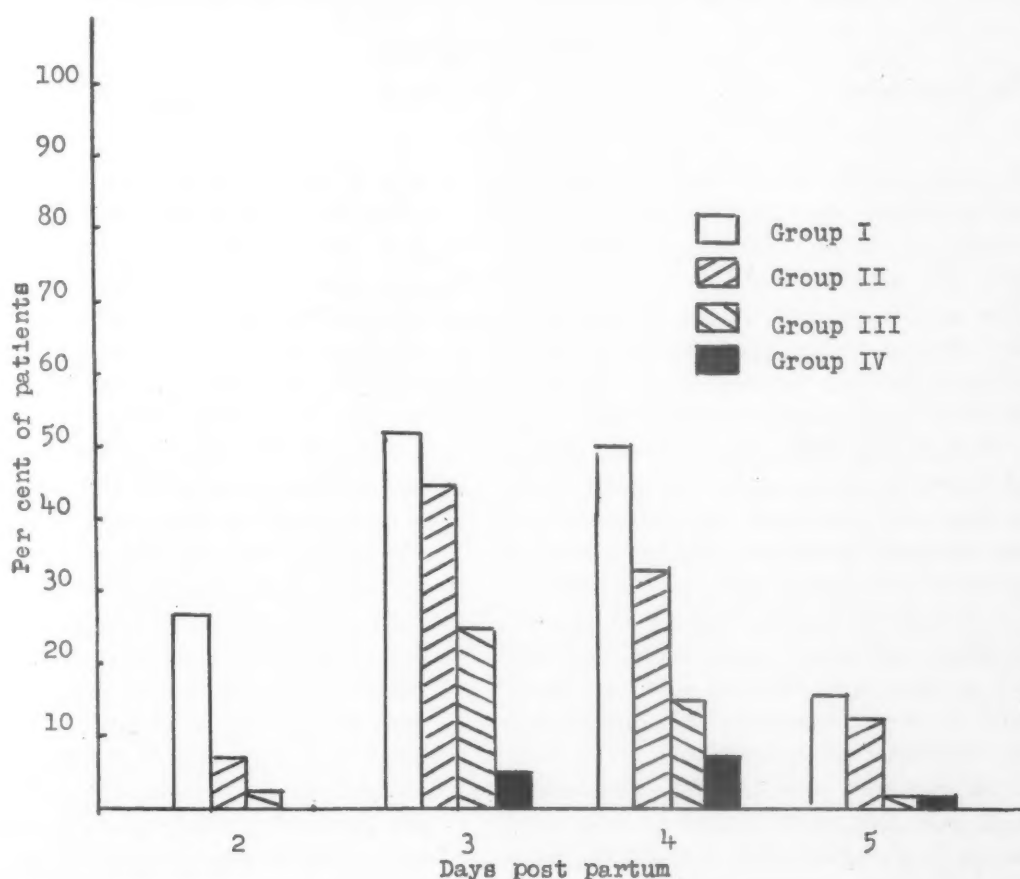


Fig. 3. Engorgement.

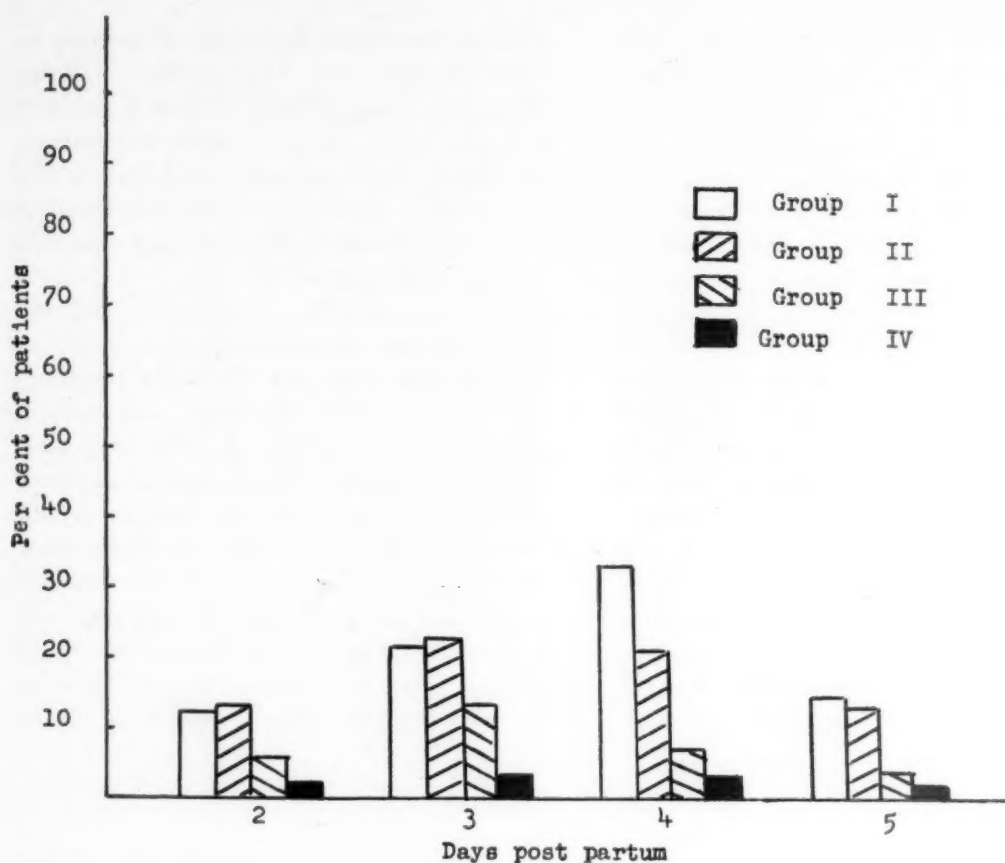


Fig. 4. Lactation.

IV experienced almost negligible amounts of lactation, the highest number being equally divided between Days 3 and 4, but only 3.8 per cent on each of these days. This would indicate that a dosage of 5.0 mg. three times daily is almost completely effective for the suppression of the actual secretion from the mammary gland.

A fourth measurement as to the efficacy of this drug was compiled with use of the number and percentage of patients requiring therapy in addition to the hormonal product itself. Such measures included the use of binders, ice bags, fluid restriction, and analgesics for symptomatic relief. As stated before, these were reserved only for patients who developed symptoms not controlled by the hormonal preparation and, when additional measures were ordered, records were kept as to the methods used and the number of days required. Fig. 5 shows the number of patients requiring additional meas-

ures of one or more types to alleviate any symptoms or findings. Here again the pattern between the control group of patients and those receiving one tablet per day is almost identical. Again following the typical pattern, there was a sharp decline in the necessity for additional supportive measures in both the Group III and Group IV patients. The difference in these two groups is statistically insignificant. Thus, it seems there is no particular advantage to a three-times-a-day dosage with regard to the requirements for additional supportive measures.

The final analysis of the efficiency of this drug was done by means of the postpartum follow-up cards, which were returned by most of the patients after the completion of the first menstrual period, usually within 6 weeks after delivery. In this method of survey the reports were generally good regardless of the treatment given in the hospital. No evidence of masculinization was reported



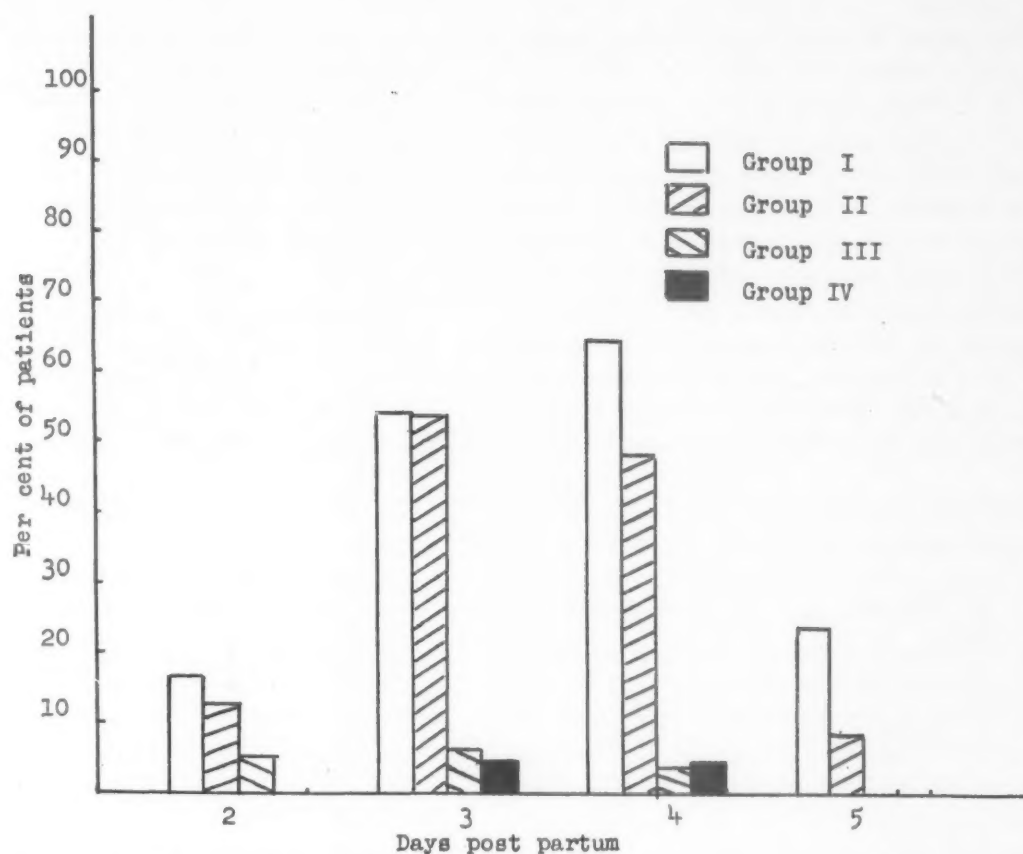


Fig. 5. Analgesics, ice bags, binders, etc., used.

by any patient, nor was there any particular delay in the onset of the first menstrual period. It would seem, therefore, that once the breast secretions have been effectively inhibited they tend to remain that way without secondary filling or lactation.

#### Comment

The suppression of lactation has been undertaken by many various methods in the past, both hormonal and nonhormonal. The present study indicates that the nonnursing patients are more comfortable with fewer annoying symptoms when treated by hormones. From the reports in the literature<sup>1, 2, 3, 5</sup> and from our own experience we have concluded that most hormones, regardless of type, will give satisfactory results. The present study substantiates this. The trend can be seen in progressive dosage forms and would seem to indicate that a

sufficiently high titer of the hormone is necessary to suppress the lactogenic hormone from the anterior pituitary gland.

It is our belief that fluoxymesterone given in dosages of 5.0 mg. daily is of little more value than no hormonal therapy at all. However, when the dose is increased to 5.0 mg. twice daily, this preparation is as efficient for the suppression of lactation as other hormones reported, both estrogenic and androgenic.<sup>1, 5</sup> If the dose is further increased to 5.0 mg. three times a day, the results are even better. This study further indicates that this preparation is without side effects, virilization, or other untoward symptoms that are occasionally found with hormonal preparations.

#### Summary

1. One hundred ninety-three cases have been studied with regard to the ability of a new halogenated derivative of testosterone

to suppress lactation in the immediate postpartum period.

2. A brief discussion of the present methods of suppression of lactation is presented.

3. With use of three groups of patients on different dosage regimes and a fourth group as a control, comparisons are made with regard to the presence of breast pain, engorgement, lactation, and the requirements for additional supportive measures.

4. The optimum dosage was determined to be a 5.0 mg. tablet three times daily for 4 but not more than 6 days, beginning as

soon after delivery as the patient can tolerate fluids by mouth.

5. No side effects or virilization were noted in any case, either during the period of administration or after discharge from the hospital as determined by follow-up correspondence with the patients.

We are indebted to the attending staff members under the supervision of Dr. George A. Hahn, for their help in this study.

We thank Ciba Pharmaceutical Products Inc. for the generous supplies of Ultandren.

---

#### REFERENCES

1. Dodek, S. M., Friedman, J. M., Soyster, P. A., and Marcellus, H. L.: *J. A. M. A.* 154: 309, 1954.
2. Kurzrock, R., and O'Connell, C. P.: *Endocrinology* 23: 476, 1938.
3. Laufe, L. E., and McCarthy, J. J., Jr.: *Pennsylvania M. J.* 59: 914, 1956.
4. Paschkis, K. E., Rakoff, A. E., and Cantarow, A.: *Clinical Endocrinology*, New York, 1954, Paul B. Hoeber, Inc., p. 515.
5. Roland, M., Veprovsky, E., and Linhart, W.: *AM. J. OBST. & GYNEC.* 70: 1004, 1955.

# Effects of mercury on human gestation

JOSE F. AFONSO, M.D.

RUSSELL R. DE ALVAREZ, M.D.

Seattle, Washington

MERCURY was known to exist in pre-historic times but it was not until about 400 B.C. that its compounds are said to have been used therapeutically in Greece, India, and Persia.<sup>1</sup> During the fifteenth and sixteenth centuries, mercurous chloride was introduced as a diuretic and later became the most popular cathartic. During the mercury era of syphilotherapy (1493 to 1909), colloidal mercury and inorganic mercurial salts were initially employed and were finally replaced by organomercurials in the latter half of the nineteenth century. With the advent and acceptance of the germ theory of disease, mercuric salts promptly became popular antiseptics and disinfectants. Koch (1843-1910) regarded them as potent germicides and contributed greatly to their widespread use. Elemental mercury and its inorganic salts soon were in common use as diuretics, cathartics, germicides, fungicides, and antisiphilitic agents. With the advent of less toxic organomercurials, the use of elemental mercury and its inorganic salts decreased considerably and later on was largely abandoned.<sup>2, 3</sup>

In modern therapy the inorganic mercurial salts seldom are employed and then only as antiseptic ointment or as disinfectants. The organic mercurial compounds are

frequently used as topical antiseptics and constitute the most powerful and reliable diuretic agents.<sup>2, 3</sup>

The toxicity of the mercurial compounds used in the past overshadowed their clinical effectiveness. While severe toxicity, even to the point of death, followed the use of mercuric chloride in vaginal douches,<sup>4-9</sup> less serious poisoning not uncommonly complicated the treatment of syphilis or constipation with inorganic mercuric salts.<sup>3, 6</sup> Occupational mercuric poisoning was described as early as the sixteenth century.<sup>6</sup> The accidental or suicidal ingestion of mercuric chloride frequently accounted for acute intoxication and death. The original descriptions of the toxicology of mercury considered it to be a general protoplasmic poison, producing precipitation of cellular proteins. This concept persisted until the discovery of a single basic mechanism of action for all dissociable mercurial compounds. At the present time, it is generally accepted that mercury ions react with sulfhydryl groups to form mercaptides. Sulfhydryl enzymes are inactivated, thus altering cellular metabolism and function. If the inactivation of these enzymes persists sufficiently long, cellular death eventually occurs.<sup>3, 10, 11</sup>

Even though some textbooks<sup>8, 12-14</sup> list mercury as a cause of abortion, very little is really known of the effects of mercury upon the growing human embryo. It is known, however, that abortion frequently occurred in syphilitic mothers treated with mercurials but whether the abortion was due to the syphilis or to its treatment has not been clarified. Search of the literature fails to disclose a single proved or even well-

*From the Department of Obstetrics and Gynecology, University of Washington School of Medicine, and the King County Hospital.*

*The investigation was supported, in part, by a grant from the Pacific Northwest Obstetrical and Gynecological Society.*

*Presented before the Seattle Gynecological Society, Seattle, Washington, May 20, 1959.*

Table I. Daily record of intake, output, and water balance

Hospital day	Intake						
	Dextrose in water (ml.)			Na (mEq.)	K (mEq.)	Cl (mEq.)	Oral water (ml.)
	50%	20%	10%				
1†		720					720
2	100	400					500
3	950						950
4	100	500		5			600
5	650			45			650
6	650			70			650
7	650			80			650
8	450			45			450
9	800			105			800
10	1,000			100			1,000
11	450			45			450
12	200		2,000	163		150	350
13			2,300	150	26	176	
14			4,200	150	54	204	400
							4,600

\*Water of oxidation estimated at 300 ml. per day.

†Insensible loss estimated at 750 ml. per day.

‡Sixth day after ingestion of mercuric chloride.

documented case of abortion or fetal intoxication due to mercury. Two cases reported by French authors were inconclusive. In one instance<sup>15</sup> the mother died after aborting. While a vague history of ingestion of a mercuric salt and a clinical picture suggesting maternal intoxication were recorded, no toxicologic or histologic studies were carried out. In their second<sup>16</sup> case, the mother suffered from occupational mercuric poisoning during two successive pregnancies. The first pregnancy resulted in a neonatal death and the second in a stillbirth. Both infants showed hepatosplenomegaly and a picture believed by the authors to represent erythroblastosis due to mercury. Toxicologic examination of these infants, however, failed to reveal mercury.

Because of the lack of a previously proved case, we felt it desirable to report herewith an instance of abortion of a 10 weeks' gestation due to acute intoxication with bichloride of mercury.

#### Case report

**Present illness.** Mrs. E. C. (No. 366060), a 31-year-old divorced white woman, gravida ix, para viii, was referred to the King County Hospital on April 26, 1958, for the management of acute renal failure.

The last menstrual period occurred on Jan. 28, 1958. No vaginal bleeding or uterine cramps had been noted since then. After missing the expected menses in February, 1958, the patient noted morning sickness, enlargement and tingling of the breasts, and increased urinary frequency. Because she thought she was pregnant, she ingested 5 tablets (0.5 Gm. each) of mercuric chloride on April 21, 1958, with the intention of inducing abortion. Immediately afterward, severe abdominal pain and fainting occurred. The patient was taken to a local hospital where gastric lavage was performed and dimercaprol was administered intramuscularly for a period of 2 days. She developed severe nausea, vomiting, hematemesis, profuse bloody diarrhea, generalized abdominal cramps, hematuria, and progressive oliguria. Forty-eight hours after the ingestion of the mercuric chloride, complete anuria ensued for which she was treated in her local community. Because of failure to respond to the treatment for acute renal failure, she was transferred to the King County Hospital 3 days later.

**Past history.** The patient had had childhood chickenpox and measles and, at the age of 17 years, rheumatic fever. She had had 8 full-term normal, spontaneous deliveries, the last one 4 years prior to the present illness. The infants weighed between 6 and 8 pounds; all were living and well. During the first and last pregnancies, she had mild toxemia of pregnancy.



Output				Total intake plus water of oxidation*	Total output plus insensible loss†	Water balance
Urine (ml.)	Stool (ml.)	Emesis (ml.)	Total (ml.)			
	100	0	100	1,020	850	+170
	200	200	400	800	1,150	-350
	400	200	600	1,250	1,350	-100
	100	100	200	900	950	-50
	100	100	200	950	950	0
	200	100	300	950	1,050	-100
	300	200	500	950	1,250	-300
	300	150	450	750	1,200	-450
30	600	0	630	1,100	1,380	-280
75	700	100	875	1,300	1,625	-325
400	500	200	1,100	750	1,850	-1,100
1,200	450	500	2,150	2,850	2,900	-50
2,600	400	200	3,200	2,600	3,950	-1,350
2,000	600	0	2,600	4,900	3,350	+1,550

**Physical examination.** At admittance, examination revealed a slightly obese, normal-appearing white woman in mild distress from generalized abdominal cramping. The blood pressure was 146/60; the pulse was 88 and regular; the temperature was 100.4° F., and the respirations regular at 20 per minute. The skin was dry with multiple punctate petechiae over the anterior surface of the trunk. A few teeth were carious and a few were absent. The buccal and pharyngeal mucosae were slightly reddened; there was no abnormal odor or salivation. The eyes, ears, and nose showed no abnormalities. The neck was normal. The breasts were pendulous with pigmented areolae and without abnormalities. Both lung fields were normal to percussion and auscultation. The heart was not enlarged. There was a normal sinus rhythm; the heart sounds were normal with a Grade III systolic murmur of equal intensity over the entire precordium, without radiation. The abdomen was not distended. The bowel tones were hypoactive. The panniculus was thick, and there was generalized abdominal tenderness without rigidity or rebound. The liver, kidneys, and spleen were not palpable, and there were no palpable abnormal masses. The extremities revealed a trace of pretibial edema bilaterally. There were no abnormal spinal curvatures or costovertebral angle tenderness. Neurological examination showed normal findings; the deep tendon reflexes were symmetrically normal.

**Pelvic examination.** The external genitals, the Bartholin and Skene glands, and the urethra were normal. The introitus was parous with a first degree cystocele. There was no bleeding or discharge. Speculum examination revealed the vagina to be bluish without visible lesions. The cervix was parous, hypertrophied, congested, and covered with a small amount of epithelial discharge, with a closed external os and without visible lesions or bleeding. On bimanual examination the vagina was found to be normal; the cervix was soft and smooth with closed external os, and was freely movable without tenderness. The fundus was anteroфлекed, globular, soft, enlarged to the size of a 10 weeks' intrauterine gestation, nontender, movable, and of normal contour. The ovaries were poorly outlined because of the size of the uterus. No abnormal masses were felt in the adnexal regions. Rectal and rectovaginal examination showed no abnormalities. The stools were guaiac positive.

**Laboratory examination on admittance.** The hematocrit level was 29 per cent; white blood count, 3,450 (65 per cent segmented, 19 per cent stabs, 12 per cent lymphocytes, 1 per cent monocytes, 1 per cent eosinophils, and 1 per cent basophils). The amount of urine obtained on catheterization was insufficient to determine the specific gravity but showed granular casts, oval fat bodies, and few gram-positive cocci, and was loaded with red and white blood cells. There was no sugar, and the proteinuria was 20 mg.

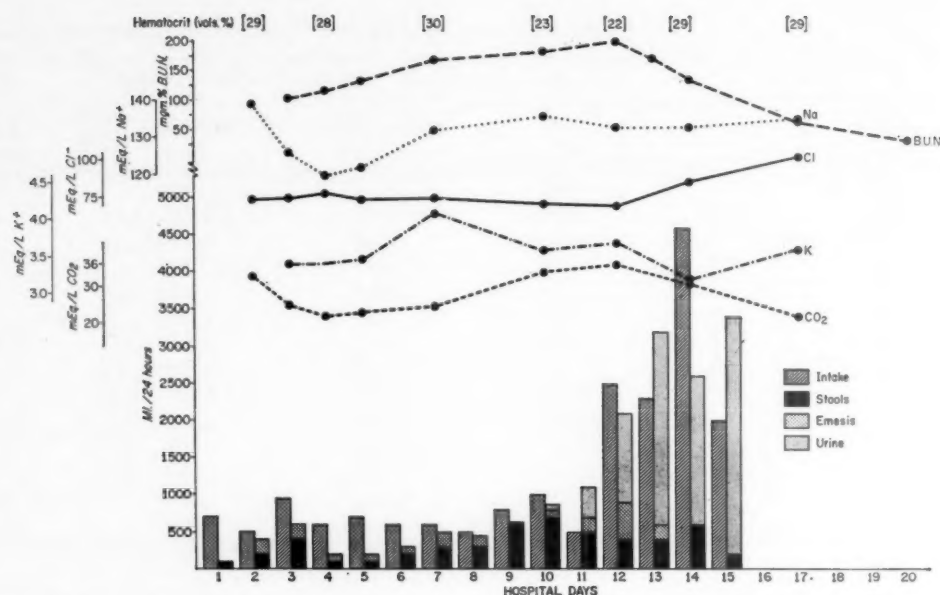


Fig. 1. Daily record of intake and output; values of serum sodium, potassium, chloride, carbon dioxide combining power, blood urea nitrogen, and hematocrit.

per cent. The serum sodium was 139 mEq. per liter, chloride 74 mEq. per liter, potassium 3.5 mEq. per liter, and  $\text{CO}_2$  combining power 33 mEq. per liter. The blood urea nitrogen was 104 mg. per 100 ml. Chest x-ray examination revealed a small zone of infiltrate in the upper lobe of the right lung and a normal configuration of the heart. The electrocardiogram was normal.

**Hospital course.** On admittance the patient was placed at bed rest, with nothing by mouth, and was started on strict fluid and electrolyte balance. She complained of generalized abdominal cramps, nausea, and vomiting. Severe diarrhea, occasionally blood tinged, was noted. She was completely anuric. A vena cava catheter was inserted and 50 per cent dextrose with added insulin (20 units per 200 c.c. of 50 per cent glucose), vitamin C, B complex, and vitamin A were administered. The exact type of daily fluid and electrolyte administration is shown in Table I. Accurate intake and output were recorded, and serum electrolytes, BUN, and hematocrit were followed closely (Fig. 1). A program of negative water and chloride balance was established and maintained throughout the phase of anuria (Fig. 2). The patient lost weight progressively (Fig. 2). The potassium balance was not determined but was certainly negative; its administration was withheld until the diuretic phase. Sodium was administered in the form

of sodium lactate beginning on the fourth hospital day to control acidosis and to replace the uncontrolled loss through the gastrointestinal tract (Fig. 2). The patient's condition remained unchanged during the first 8 hospital days except for the appearance of slight confusion and disorientation as the BUN rose from 104 to 164 mg. per cent. Promazine was unsuccessful in alleviating nausea. Abdominal pain was relieved by codeine, 60 mg. every 6 hours. The blood pressure, temperature, and pulse remained normal. On the afternoon of the eighth hospital day, 13 days after the ingestion of the mercuric chloride, uterine cramping and vaginal bleeding began. On this date the patient was examined and a 5 cm. fetus and placenta were found in the vagina and removed. The uterus was quite firm and had decreased to the size of a 6 weeks' gestation; there was a slight amount of uterine bleeding coming through the cervix. The fetus appeared to be 10 weeks old, was not macerated, and was grossly normal. The placenta was thought to be complete and no abnormalities were noted. The total blood loss was estimated to be 300 ml. During the subsequent 4 days a small amount of vaginal bleeding occurred requiring 1 or 2 pads per day. The hematocrit level remained stable from the time of admission, varying between 28 and 30 per cent, but 2 days after the abortion had decreased to 22 per cent. Five hundred milliliters of whole blood was

given, raising the hematocrit level to 29 per cent. No oxytocics were administered. Procaine penicillin was given prophylactically for 5 days in the dosage of 600,000 units twice daily. On the ninth hospital day, 14 days after the ingestion of mercuric chloride, urinary output was noted for the first time since admission, a total of 30 ml. per 24 hours. The diarrhea and vomiting increased. The urinary output rose slowly (Fig. 1), increasing to a volume of 1,200 ml. per 24 hours on the twelfth day. During the diuretic phase the volume of fluids administered was increased to 3,000 to 4,000 ml. daily; 40 to 60 mEq. of potassium chloride and 150 mEq. of sodium chloride were given daily. On the sixteenth hospital day the temperature rose to 101.4° F., and the urinalysis showed evidence of urinary tract infection by the presence of 10 to 15 leukocytes with clumps, bacteria, and proteinuria. Urine culture grew coli aerogenes sensitive to chloramphenicol. Chloramphenicol, 500 mg. four times a day, was given orally for 5 days with good response. The BUN decreased

slowly to 36 mg. per cent by the nineteenth hospital day (Fig. 1). On the sixteenth hospital day the nausea, vomiting, and diarrhea subsided, and the serum electrolytes returned to normal. On the twentieth hospital day the patient felt quite well. Temperature, blood count, and urinalysis were normal. She refused the recommended renal function studies and left the hospital against medical advice. She returned to her local community and has not been seen since.

### Comment

The clinical picture herewith presented typifies acute mercuric chloride intoxication. Pain, inflammation, and swelling of the oral and pharyngeal mucosa, acute abdominal pain, nausea, and vomiting developed within minutes after the ingestion of the mercury. Bloody diarrhea and hematemesis occurred during the next 24 hours and persisted for about 16 days. Hematuria and oliguria began during the first 24 hours and rapidly

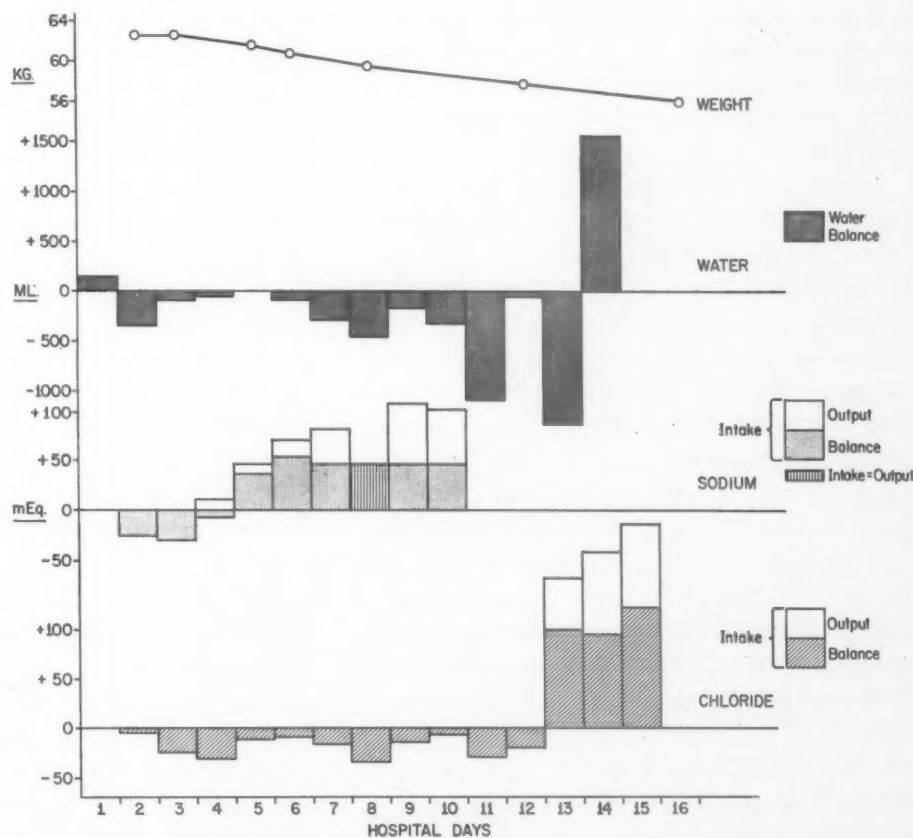


Fig. 2. Weight changes and daily water, sodium, and chloride balances.

progressed to complete anuria within the next 24 hours.

These symptoms and signs reflected epithelial damage at the portals of absorption (upper gastrointestinal mucosa) and excretion (colon and kidney) of the mercury. Mercury is absorbed from the gastrointestinal tract, vaginal mucosa, lungs, and skin.<sup>3, 7, 8, 11</sup> Once it has gained access to the systemic circulation, it is rapidly taken up by the tissues. The exact form in which ionic mercury circulates and is deposited in tissues is not known. The principal reaction is with thiols with formation of mercury mercaptide.<sup>3, 10, 11</sup> It is quite likely that the distribution of mercury involves transport by serum mercaptalbumin (containing 5 to 10 per cent of the total thiol content of human plasma<sup>3, 10</sup>). Mercury could leave the blood stream in combination with one of the small, diffusible thiols and be exchanged to proteins of even higher avidity within the cell.<sup>10</sup> Mercury is impounded in all tissues, particularly liver, kidney, spleen, and bone, where high preferential concentrations are found.<sup>3, 7, 10</sup> It is excreted quite rapidly, mainly through the urine and the feces, but may also be found in sweat and in milk.<sup>3, 7, 11</sup>

Mercuric chloride is the most dangerous compound to gain access to the circulation. While the mean lethal dose varies between 1 and 4 Gm., fatalities have been reported following ingestion of 500 mg.<sup>7, 17</sup> Death can occur within hours or even minutes as a result of shock. During the first 2 weeks after ingestion, death usually results from uremia and thereafter from hepatitis or colitis.<sup>6, 7, 8, 17</sup> Even though our patient ingested between 2 and 2.5 Gm. of mercuric chloride she survived, most likely because of prompt institution of therapy. The pathologic changes observed in the gastrointestinal tract usually consist of necrosis of the epithelium with swelling, inflammation, and desquamation.<sup>3, 7, 8</sup> The liver reveals cloudy swelling of the hepatic parenchyma and lobular ischemia from mechanical reduction of the sinusoidal lumina.<sup>7, 18</sup>

Myocardial damage is reportedly infre-

quent and was not present in our case. Petechial hemorrhages, dermographism, and eczema usually occur as a result of chronic poisoning.<sup>3, 8</sup> While the latter two manifestations were absent in our patient, she did present punctate petechiae over the entire surface of the trunk but without evidence of thrombocytopenia or other abnormality of blood coagulation.

Complete anuria appeared 48 hours after ingestion of the mercuric chloride and lasted for a total of 14 days. After the resumption of renal function, oliguria persisted from the fifteenth through the seventeenth day followed by the output of normal urine volumes thereafter.

Accordingly, with the concepts expressed by Oliver and associates,<sup>19, 20</sup> the initial renal lesion produced by mercuric poisoning consists of diffuse nephrotoxic damage of the proximal tubule with necrosis of the epithelium. This necrosis may extend throughout the entire length of the proximal tubule from the glomerulus to the descending loop or may affect selectively only the distal portion of the proximal tubule depending upon the amount of mercury ingested. The second described lesion has been called tubulorrhexis and consists of disruption of the continuity of the tubule; it may be found anywhere in the nephron. This occurs as a result of renal ischemia and may be due to the profound circulatory collapse that follows acute mercurialism. On the other hand, it may occur as a result of a direct vasoconstrictive action of mercury upon the efferent glomerular arteriole as observed in induced intoxication in rats.<sup>18</sup> The degree of recovery of renal function in the case reported is not known because the patient refused the tests proposed.

The pregnancy seemed undisturbed on admission. The size of the uterus was compatible with the duration of the amenorrhea and presented no signs or symptoms of impending abortion. It was not until 13 days after ingestion of the mercuric chloride that the onset of vaginal bleeding and uterine cramps was noted, followed by spontaneous delivery of a nonmacerated normal-ap-



pearing 5 cm. fetus and placenta. In view of the potential vasoconstrictive effect of natural and synthetic alkaloids of ergot neither ergonovine maleate (Ergotrate) nor methyl-ergonovine tartrate (Methergine) was prescribed. Because of the imminent renal failure, the common hepatic lesions, and possible vasoconstriction of the efferent glomerular arteriole, we feel that ergot alkaloids should not be used in patients with acute mercuric poisoning. Patients with uremia often present a generalized bleeding tendency and poorly understood abnormalities of blood coagulation; therefore, an unusual amount of blood loss may occur following an abortion, as a result of the abortion or simply from gastrointestinal bleeding. If oxytocics must be used, one offering the least degree of vasoconstriction should be selected; synthetic oxytocin (Syntocinon) would seem to be the drug of choice. In this patient the total blood loss during the abortion was estimated to be 300 ml., with only slight vaginal spotting during the following 4 days. Even though the exact mechanism for the production of the abortion is not known, three possible explanations seem plausible: (1) the abortion was caused by uremia, (2) it was due to mercuric damage of the placenta or fetus, or (3) it was spontaneous and unrelated to the ingestion of mercury and its sequelae.

While it is commonly asserted that severe uremia can and does cause abortion, no documented cases have been reported to support this contention. The blood urea concentration of the fetus is usually similar to that of the mother; since the concentration is equal on both sides of the placental barrier it appears that urea crosses the placenta by simple diffusion. However, urea per se is nontoxic. Neither hyperkalemia nor acidosis of appreciable degree was noted in our patient. Even though the toxic substances responsible for the uremic syndrome are not known, those agents presently incriminated (organic acids, magnesium, polypeptides of low molecular weight) could themselves easily pass the placental barrier and contribute to fetal death and subsequent abor-

tion. Whatever they are, these substances can be dialyzed as proved by the excellent results following extrarenal dialysis of uremic patients. Therefore, these toxic substances could cross the placenta by simple diffusion and produce abortion.

As a result of studies of tissue cultures of embryonic chick heart, rabbit spleen, human spleen, and lymph glands, it is known that embryonic and adult tissues are affected by mercury. Complete inhibition of cellular growth and death were found when the cells were exposed to mercuric chloride in dilutions as small as 1:45,000 to 1:80,000. In our experimental work in rats, we have found that, following the administration of mercuric chloride by gastric intubation or intramuscular injection, nonfatal intoxication of the pregnant animal can be induced. This is followed by abortion or neonatal death of the litters. We have failed so far to identify placental or fetal lesions due to mercury but we have proved the placental transfer of this metal. This work is still in progress and it will be reported at a later date. Perhaps the answer is even simpler by virtue of the fact that mercury with a molecular weight of about 400 should be expected to cross the placental barrier by diffusion and thus affect the fetus directly. The alterations produced by mercury in the structure and function of the human fetus or placenta are not known. As already stated, mercury inactivates sulfhydryl enzymes and interferes with cellular metabolism and function, producing cellular death. It seems reasonable to assume that this effect would strongly alter placental function in view of the large number of sulfhydryl enzymes present in this organ and would indirectly interfere with fetal growth and development.

Careful histologic study of the fetus and placenta was performed in our patient, but failed to reveal any significant lesions; thus, we must state that no alteration of structure was present.

Toxicologic examination of the fetus was carried out by the Department of Pharmacology by means of the Dithizone method

with modifications. Mercury was found in a concentration of 20  $\mu\text{g}$  per 100 grams of fetal tissue. Determinations of mercury for control purposes carried out in two 10-week-old fetuses revealed 4  $\mu\text{g}$  of mercury per 100 grams of fetal tissue in one and no mercury in the other. There are no other values available to show what the normal concentration of mercury is in the human fetus or placenta.

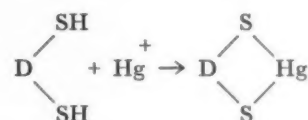
The possibility of the abortion being spontaneous and unrelated to the mercuric intoxication seems very remote in view of the past obstetrical history, lack of evidence of abnormal embryogenesis, the presence of uremia, and especially the abnormal concentration of mercury found in the fetus. The concentration of mercury (20  $\mu\text{g}$  per cent) found in the fetus can be considered toxic. It is our considered opinion that this abortion was caused by mercurial intoxication of the fetus and probably of the placenta even though uremia could have been an important contributing factor.

When faced with a similar problem one must consider what can be done in order to salvage not only the mother but the fetus as well. The principal objective is to prevent mercury from reaching the maternal and fetal body cells and combining with cellular enzyme systems vital to existence. To accomplish this, mercury present in the gastrointestinal tract must be inactivated and removed. Protein in the form of milk, raw eggs, or ground meat should be given.<sup>3, 7, 8, 22</sup> Large amounts of warm sodium bicarbonate should be administered, and vomiting produced by mechanical or pharmacologic means. If sodium formaldehyde sulfoxylate is available, the stomach should be lavaged with 1,500 to 2,000 c.c. of a 10 per cent solution.<sup>3, 7, 22</sup> Both protein and sulfoxylate combine with mercuric ions. Protein acts by fixing the ion to the sulfhydryl groups while the sulfoxylate reduces the mercuric ion to the less soluble mercurous form.

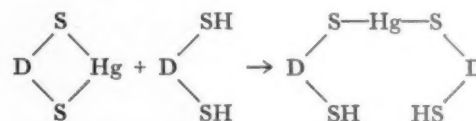
The immediate administration of BAL (2, 3-dimercaptopropanol) is mandatory in order to inactivate the mercury already

absorbed. Three to five milligrams per kilogram of body weight should be given intramuscularly every 4 hours for 2 days and twice daily for 10 days or until recovery.<sup>7, 22, 23</sup> Longcope and his associates<sup>24</sup> recommend BAL be given in an initial dose of 300 mg. intramuscularly followed by 2 or 3 injections of 150 mg. within the first 2 hours; during the next 12 hours 1 or 2 injections of 150 mg. are given followed by the daily administration of 150 to 300 mg. for 1 or 2 days.

If acute renal insufficiency develops, BAL therapy should be discontinued or given in very small doses. Under such circumstances, BAL is not excreted in appreciable amounts and its serum concentration rises to toxic levels as shown by Doolan, Hess, and Kyle.<sup>25</sup> BAL should also be used cautiously in cases of extensive hepatic insufficiency.<sup>3</sup> BAL, a dithiol, reacts with mercury to form cyclic mercaptides of low dissociability.<sup>3</sup>



These mercaptides will react with an additional mol of BAL to form the even less dissociable di-BAL complexes.<sup>3</sup>



BAL is effective in that it protects the cellular sulfhydryl enzymes from inactivation by mercury and also reactivates enzyme systems already inhibited.<sup>3</sup>

Circulatory collapse should be prevented by correction of dehydration and electrolyte loss. Electrolyte studies should be performed carefully and regularly and balance maintained. If renal failure is present, care should be taken to prevent hyperkalemia, acidosis, and water intoxication. Fluids should be restricted, with the water of oxidation and the anticipated losses through the lungs, skin, vomiting, and diarrhea taken into consideration. Large amounts of glucose with

insulin should be administered intravenously (usually through the catheter inserted into the vena cava) in order to prevent protein breakdown and to forestall uremia as well as hyperkalemia. Testosterone may be used to prevent hyperkalemia, and acidosis should be corrected with intravenous administration of sodium lactate. If hyperkalemia occurs or uremia becomes a really severe problem, lifesaving extrarenal dialysis should be instituted.

We know of no other drugs or procedures that could be used to prevent fetal death and/or abortion. Prophylaxis is important when one considers the possibility of exposure to mercury of a pregnant woman. Even though acute mercuric poisoning is not frequent and usually is caused by accidental or suicidal ingestion, it is important that the gynecologist keep in mind the possibility that abortion may be on this basis, particularly when acute renal failure supervenes. Chronic poisoning is almost solely an occupational disease, and it will continue to present a problem as new uses for mercury are found in the newly developed fields of electronics, casting processes, and nuclear physical research. It is obvious that pregnant women should not be employed in occupations where they are exposed to mercury, such as in the manufacture of fur felt hats or dry cell electrical batteries, in the field of electronics, or in certain laboratories. On

the other hand, modern organic mercurial diuretics (such as chlormerodrin, meraluride, etc.) can be used relatively safely in pregnant women in therapeutic dosage without great fear of fetal or maternal toxicity.

#### Summary

1. A case of acute mercuric intoxication occurring in the tenth week of pregnancy is presented.
2. It is believed that the abortion occurred as a result of intoxication of the fetus and placenta by mercury.
3. Mercury produces abortion possibly through the inactivation of placental sulfhydryl enzymes; fetal death may occur directly from fetal intoxication or indirectly from placental failure.
4. Uremia can conceivably cause abortion through the production of acidosis or placental transfer of the unknown toxic agents responsible for the azotemia.
5. A summary of the pharmacology and toxicology of mercuric compounds is presented.

We wish to express herewith our gratitude to Dr. Demetri Tsilifonis and Dr. Ted Loomis of the Department of Pharmacology for the toxicologic studies and to Dr. Irving Schuldberg of the Department of Pathology for his assistance in the histologic examinations.

#### REFERENCES

1. King, C. V.: *Ann. New York Acad. Sc.* 65: 369, 1957.
2. Friedman, H. L.: *Ann. New York Acad. Sc.* 65: 461, 1957.
3. Goodman, Louis S., and Gilman, Alfred: *The Pharmacological Basis of Therapeutics*, New York, 1955, The Macmillan Company, p. 973.
4. Marcel, J. E., and Abaza, A.: *Compt. rend. Soc. franç. gynec.* 19: 199, 1949.
5. Pacchiani, G.: *Gior. sc. med.* 1: 43, 1946.
6. Goldwater, Leonard J.: *Ann. New York Acad. Sc.* 65: 498, 1957.
7. Thienes, H. C., and Harley, T. J.: *Clinical Toxicology*, Philadelphia, 1948, Lea & Febiger, p. 158.
8. Von Oettingen, W. F.: *Poisoning*, New York, 1952, Paul B. Hoeber, Inc., p. 385.
9. Gonzalez, Rodolfo, and Firstater, Mauricio: *Rev. argent. urol.* 17: 629, 1948.
10. Hughes, Walter L.: *Ann. New York Acad. Sc.* 65: 454, 1957.
11. Schoemaker, Harold A.: *Ann. New York Acad. Sc.* 65: 505, 1957.
12. Llusia, Jose Botella: *Patologia obstetrica*, Barcelona, 1950, Editorial Científicos Médica, p. 196.
13. Rubin, I. C., and Novak, J.: *Integrated Gynecology Principles and Practice*, New York, 1956, Blakiston Company, vol. 2, p. 37.
14. Alfaro, P. A. G., Agüero, O., Aurrecoechea, J. M., and Calcaño, J.: *Primer congreso mexicano de ginecología e obstetricia*, Mexico, May, 1949, p. 382.
15. Guilhem, P., Pontonnier, A., and Fournie, J.:

- Bull. fed. Soc. gynec. et obst. franç. 8: 242, 1956.
16. Derobert, L., Tara, S., and Leroux, M.: Ann. méd. lég. 30: 222, 1950.
  17. Gleason, M. N., Gosselin, R. E., and Hodge, H. C.: Clinical Toxicology of Commercial Products, Baltimore, 1957, Williams & Wilkins Company, p. 154.
  18. Crowson, C. N., and King, J. B.: A. M. A. Arch. Path. 64: 607, 1957.
  19. Oliver, Jean: Am. J. Med. 5: 535, 1953.
  20. Oliver, Jean, MacDowell, Muriel, and Tracy, Ann: J. Clin. Invest. 30: 1307, 1951.
  21. Salle, A. J., and Lazarus, A. S., Proc. Soc. Exper. Biol. & Med. 34: 371, 1936.
  22. Ryder, Henry W.: Mercury Poisoning—Current Theory, Philadelphia, 1954, W. B. Saunders Company, p. 832.
  23. Brookes, Vincent J., and Jacobs, Morris B.: Poison, Princeton, N. J., 1958, D. Van Nostrand Co., Inc., p. 87.
  24. Longcope, W. T., and Luetscher, J. A., Jr.: J. Clin. Invest. 25: 857, 1946.
  25. Doolan, P. D., Hess, W. C., and Kyle, L. H.: New England J. Med. 249: 273, 1953.



# Spontaneous rupture of the liver during pregnancy

Case report and review of the literature

ALLAN B. WEINGOLD, CAPTAIN, MC, USA \*

JAMES W. THOMPSON, MAJOR, MC, USA

*New York, New York*

SPONTANEOUS rupture of the liver during pregnancy is a rare and grave complication. A review of the literature reveals 20 such cases. The clinical picture in most cases is similar, with multiparity, some degree of toxemia, abdominal pain, and shock as salient points. Most authors in the past have indicated an underlying diseased vascular system of the liver as the cause of this condition. The object of this paper is to present a case report of spontaneous rupture of the liver in pregnancy which closely parallels previously reported cases. A review of the literature is included to emphasize that this is a rather characteristic clinical entity requiring early recognition to avoid a fatal outcome.

## Review of the literature

**Incidence.** Table I shows that the ages range from 24 to 42 years. The average of 33 years is high for a random group of obstetrical patients, and this is consistent with the multiparity present in all except one case. Although this accident was reported by Links<sup>11</sup> in a patient 4 months gravid, the majority of the patients were pregnant 34 to 40 weeks. Of the 19 cases in which the outcome is known, there have been 5 survivals, and each of these patients underwent surgical intervention (2 during the immediate post-

partum period). It would appear that this is indeed a grave complication and that early recognition and rapid surgical therapy are the only means of obviating fatalities.

**Etiology.** Devic<sup>21</sup> first used the term "apoplexie hépatique" for rupture of the liver when definite trauma can be excluded. In this instance, intrahepatic hemorrhage causes the rupture whereas in traumatic rupture hemorrhage follows the injury.

Although all the cases reviewed are classified as spontaneous ruptures the majority of authors have mentioned minor degrees of trauma as etiological factors. The first reported case, that of Abercrombie<sup>1</sup> in 1844, could be considered of traumatic origin. The catastrophe was associated with the tight application of a silk handkerchief around the upper abdomen by a maid-servant for the relief of gastrodynia. Burton-Brown and Shephard<sup>12</sup> believed that the injury in their patient was the result of local trauma produced by violent contractions of the diaphragm and abdominal muscles in labor. Haller<sup>13</sup> noted that the strain that occurs with convulsions (which were present in 6 of the cases) could be a traumatic factor, and Sanes and Kaminski<sup>10</sup> suggested that rupture in their patient seemed to follow a sustained uterine contraction produced by Pitocin.

External trauma of insignificant degree that is engendered by transportation of the patient from bed to stretcher to delivery table or by abdominal palpation during labor cannot be definitely excluded as a precipitat-

*From the Obstetrics and Gynecology Service, Rodriguez United States Army Hospital, Fort Brooke, San Juan, Puerto Rico.*

*\*Present address: The Hospital for Joint Diseases, New York 35, New York.*

**Table I.** Chronological listing of the reported cases of spontaneous rupture of the liver

<i>Author</i>	<i>Year</i>	<i>Age of patient</i>	<i>Gravidity</i>	<i>Month of pregnancy</i>	<i>Convulsion</i>	<i>Hypertension</i>	<i>Outcome</i>
Abercrombie <sup>1</sup>	1844	35		8			Fatal
Kosoloff <sup>2</sup>	1914	39	Primipara		+	+	Fatal
Herz <sup>3</sup>	1918	41	Multipara	8	+	+	Fatal
Kolisko <sup>4</sup>	1928	24		Term	+	+	Fatal
Duverges <sup>5</sup>	1928	39	Multipara	Term		+	Fatal
Roblee <sup>6</sup>	1940		No details		+		Recovery
Roemer <sup>7</sup>	1941	30	Multipara	7		+	Fatal
Rademaker <sup>8</sup>	1943	32		8		+	Recovery
Lascarro <sup>9</sup>	1944		Multipara	6		+	Fatal
Sanes and Kaminski <sup>10</sup>	1946	26	Multipara	7	+	+	Fatal
Links <sup>11</sup>	1946	42	Multipara	4		+(?)	Recovery
Burton-Brown and Shephard <sup>12</sup>	1949	32	Multipara	Term		+	Recovery
Haller et al. <sup>13</sup>	1951	34	Multipara	8		+	Fatal
Speert-Tillman <sup>14</sup>	1952	31	Multipara	7	+	+	Fatal
Kramish et al. <sup>15</sup>	1954	32	Multipara	Term		+	Recovery
Howard and Fandrich <sup>16</sup>	1956	35	Multipara	7		+	Fatal
Pereyra and Lawler <sup>17</sup>	1956	34	Multipara	8		+	Fatal
Fazekas <sup>18</sup>	1957		No details				
Cerone and Catalino <sup>19</sup>	1958	32	Multipara	6		+	Fatal
Alons <sup>20</sup>	1958		No details				
Present case	1958	27	Multipara	8		+	Fatal

ing factor in hepatic rupture, but of greater note than the possibility of trauma in the discussion of etiology is the observation that all but 2 of the cases, with known details of rupture of the liver in pregnancy, occurred in conjunction with toxemia of some degree.

Speert and Tillman<sup>14</sup> stated that the combination of hypertension, convulsions, and vomiting was apparently adequate to raise the intra-abdominal pressure sufficiently so that rupture of Glisson's capsule by a massive subcapsular hematoma occurred. The latter probably resulted from the liver lesions of toxemia.

Rademaker<sup>8</sup> suggested that perhaps some of the sudden deaths occurring in eclampsia might be due to undiagnosed rupture of the liver. Shephard<sup>12</sup> thought that this speculation was open to doubt for, although scattered areas of necrosis and small subcapsular hemorrhages are not too infrequently found in the eclamptic liver, severe hemorrhages are not a feature of the disease per se.

Links,<sup>11</sup> Shephard,<sup>12</sup> and Kramish<sup>15</sup> felt that their patients had pre-existing subclinical pre-eclampsia, which first was apparent in the postpartum period or after shock

had been overcome, manifested by headache, dizziness, hypertension, epigastric pain, and albuminuria. A clotting defect was demonstrated in Pereyra's patient. This patient had hypertension and abruptio placentae, and subsequently developed afibrinogenemia which resulted in profuse hemorrhage from the spontaneously ruptured liver.

It would seem, however, that both unrecognized mild trauma or systemic factors such as toxemia or blood dyscrasias do not fully explain the pathophysiology of spontaneous hepatic rupture. The presence of intrahepatic vascular disease generally is accepted as the underlying factor in this entity.

**Pathology.** Eclamptic lesions constitute the primary cause for subcapsular hemorrhage of the liver. Characteristic changes occur at the periphery of the hepatic lobule with focal areas of extreme dilatation of the portal sinusoids. This may result in rupture of the sinusoids, with the extravasation of blood causing necrosis of adjacent hepatic cells. The hepatic involvement may be diffuse, differing from the focal lesions in that the plasma does not coagulate and fibrinogen practically never is seen. Whether or not this

is related to a systemic fibrinogen depletion is undetermined.

Rademaker<sup>8</sup> described the following chain of events: vascular lesion, infarction of hepatic tissue, hypervascularization at the periphery, rupture of a vessel, intrahepatic hemorrhage, rupture of tissue with subcapsular hematoma, perforation of the capsule, hemoperitoneum, and death. Speert<sup>14</sup> points out that in contrast to the young primipara who is the eclamptic prototype all but one of the patients of known parity were multiparas of advanced obstetrical age. The age and parity of this group are similar to those subject to spontaneous rupture of the uterus. Speert suggested the possible etiological importance of degenerative changes in the connective tissue as a result of aging.

Grossly, the subcapsular hemorrhage was limited to the anterior and superior surfaces of the right lobe in all of the reported cases except one. Since the intrahepatic vascular lesion is not limited to any specific area of the liver, the reason for this predilection cannot be definitely ascertained. Mild trauma may play an important role.

More common causes of spontaneous rupture of the liver are malaria, aneurysm, angiomatous tumor masses, tertiary syphilis, or typhoid fever. These conditions have not been reported in conjunction with rupture of the liver in pregnancy.

#### Case report

Mrs. P. B., a 27-year-old Negro woman, para 6-2-4-3, was admitted to Rodriguez United States Army Hospital at 4 P.M. on Dec. 30, 1958. The last menstrual period occurred on April 15, 1958, and the estimated date of confinement was Jan. 22, 1959. She complained of epigastric pain and substernal pressure radiating to the mid-back of 6 hours' duration.

**Prenatal course.** The patient had been treated in the prenatal clinic since Sept. 8, 1958, with phenobarbital and salt restriction for pregnancy complicated by hypertension. She had been hospitalized twice during this period: first, for observation of a possible premature labor, and, on the second occasion, for control of a moderate hypertension. She responded well to the addition of a reserpine derivative and Diuril to

the regime. The total weight gain was 14 pounds and urine specimens were albumin-free.

**Past history.** The patient had been treated intermittently for hypertension during the preceding 10 years without a history of cardiac involvement. Kidney function evaluations, lupus preparations, and sickling studies were negative. The obstetrical history included early spontaneous abortions in 1950 and 1953 and the delivery of a stillborn infant at 34 weeks in 1954. In 1955, 1956, and 1957 she carried pregnancies to 37 weeks and was delivered of living infants weighing 4½ to 5½ pounds. The last delivery occurred at this hospital after elective induction.

On several occasions treatment with reserpine derivatives for hypertension complicating pregnancy was accompanied by gastrointestinal complaints suggestive of peptic ulcer. Because of her almost constant gravid state radiologic studies never were performed.

**History of present illness.** At 10 A.M. on the day of admission, the patient noted the onset of epigastric pain and substernal pressure which resembled prior episodes experienced when she was on reserpine therapy. This was followed by nausea. She recalled no trauma to the thorax or abdomen. No contractions were noted but when the pain persisted and increased in severity she decided to seek hospital care.

**Physical examination on admission.** The patient was alert, afebrile, and not acutely ill. The blood pressure was 200/110; the pulse, 80. Funduscopic examination revealed Grade I hypertensive retinopathy. Abdominal palpation showed mild epigastric tenderness without rebound or muscle guarding. The uterine fundus was palpable 26 cm. above the symphysis. There was a vertex presentation and the estimated fetal weight was 4½ pounds. No other abdominal organs were palpable. Bowel sounds were hypoactive. Fetal heart tones were heard in the left lower quadrant. There was no evidence of thoracic or abdominal trauma, and the remainder of the physical examination was not unusual.

**Laboratory studies.** The hemoglobin level was 11.9 Gm. per cent; hematocrit, 38 vol. per cent; white blood count, 12,400 with a normal differential. Bleeding and clotting times were normal. The serum amylase level was 128 mg. per cent. Urinalysis revealed 3-plus albuminuria. An electrocardiogram showed nonspecific T-wave changes with no acute injury pattern.



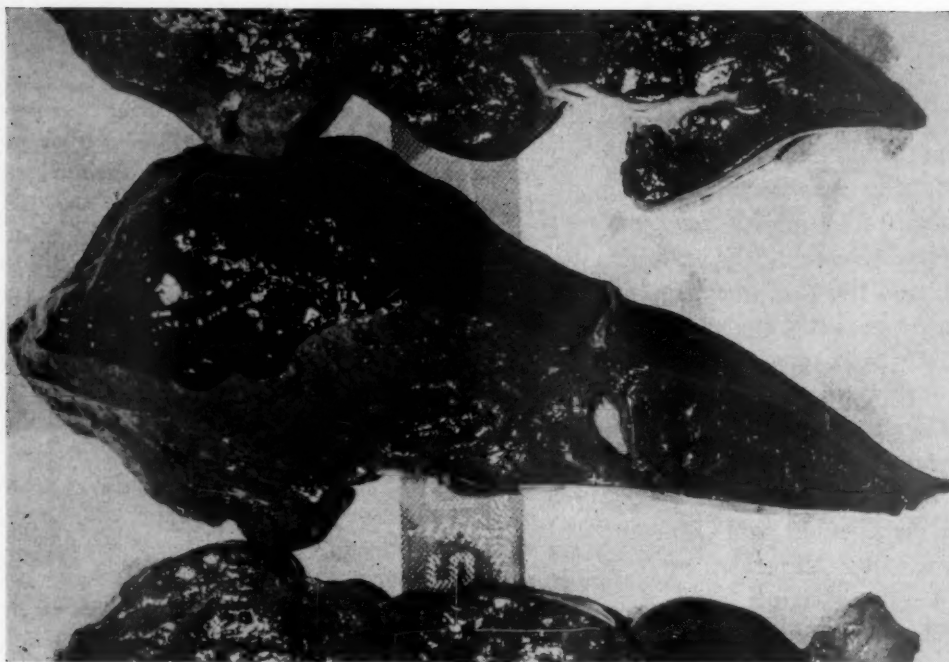


Fig. 1. Cross-section of the liver demonstrating a subcapsular hemorrhage on the anterior and superior surfaces. The multiple angiomatous spaces can also be seen in the parenchyma.

**Hospital course.** Our initial impression was that the patient had pancreatitis or a posterior penetrating duodenal ulcer secondary to reinstitution of reserpine therapy. The patient was treated with bed rest and antispasmodic and sedative medication. At 11 P.M., 7 hours after admission, having rested comfortably during this period, she vomited normal-appearing gastric contents. Immediately thereafter, she fell into profound shock with intermittently palpable rapid pulse and no audible blood pressure. The apical rate was 140 to 160. She continued alert, however, and complained of severe epigastric pain. There was no abdominal muscle guarding or rebound; tenderness was limited to the epigastrium. There was no evidence of intraperitoneal fluid. The uterus was quiet and had not increased in size but the fetal heart tones were absent almost immediately after shock had supervened. There was no vaginal bleeding. A repeat hemogram was unchanged. An electrocardiogram revealed no acute injury pattern but the diagnosis of myocardial infarction was nevertheless considered. Blood clotting appeared normal and there were no ecchymoses at puncture sites. Despite the administration of nor-epinephrine, hydrocortisone, and whole blood, which was given although there was no evidence

of blood loss, the patient failed to respond and died at 5:10 A.M. on Dec. 31, 1958.

**Autopsy findings.** Gross examination revealed no evidence of trauma of the skin, subcutaneous tissue, or bony structure of the thorax and abdomen. The peritoneal cavity contained 500 c.c. of free liquid blood. There was a large subcapsular hemorrhage of the liver over the right lobe on its superior and anterior surfaces (Fig. 1). There was an extensive laceration of the capsule measuring 15 cm. in its longest diameter. Cut section showed extensive subcapsular hemorrhage, well delineated from the underlying parenchyma which exhibited numerous poorly defined, small (1 to 3 mm.), and reddened areas irregularly distributed but more prominent near the area of hemorrhage. The spleen was intact and pancreatic and duodenal areas were not unusual. The gravid uterus contained a 4½ pound female infant and a normal placenta which showed no evidence of separation.

Microscopic examination of the liver revealed numerous areas in the periportal spaces showing a marked engorgement of the hepatic sinusoids with actual rupture of the walls forming irregularly shaped spaces filled with blood. The liver cells adjacent to these angiomatous spaces were destroyed by this process. This histologic



picture was not diagnostic, although it was suggestive of eclamptic involvement. The kidneys, which appeared normal on gross inspection, were found to present a microscopic picture compatible with nephrosclerosis or old membranous glomerulonephritis.

#### Comment

The lack of a specific hepatic lesion to explain this rare occurrence is not unexpected since most authors report a similar paucity of findings. It is possible, however, that other cases of spontaneous rupture of the liver in which histologic studies were not reported may have been due to more obvious intra-hepatic defects. In any event, it is extremely doubtful that spontaneous rupture occurs in the absence of intrinsic hepatic disease.

The striking clinical facet of the case was the sudden and profound state of shock which seemed out of proportion to the blood loss later noted at autopsy. Several authors<sup>12, 15</sup> have experienced similar situations. Our impression is that there must be some other shock-producing factor, probably of a neurovascular type, which initiated the hypotension and was potentiated by the actual hemorrhage. This may have occurred with the stripping up of Glisson's capsule by the forming hematoma or may have resulted from the peritoneal insult at the time of capsular rupture.

Primary shock of this type in acute peritonitis, visceral perforation, strangulation of bowel, and testicular injury is usually transient but may be severe and progress to an irreversible state. Specific syndromes of this nature, such as splanchnic shock<sup>22, 23</sup> and pleural shock,<sup>24</sup> have been described, but the exact pathogenetic mechanism remains unclear. The patient in uncomplicated pregnancy near term is subject to transitory hypotension, occasionally severe in degree, by assumption of the supine position. This has been described by Howard,<sup>25</sup> who thought that pressure on the vena cava was the cause. Experiments with animals have indicated possible explanations of profound shock out of proportion to blood loss. A circulating lethal toxin<sup>26</sup> in patients with hemorrhage

has been described, and aberrations in the reticuloendothelial system causing increased susceptibility to toxic and hemorrhagic shock have also been noted.<sup>27</sup> A particularly interesting thought in cases of hepatic injury is the possibility that a locally produced vasodepressor material, described by Zweifach and others, might be released in large quantities, causing peripherovascular collapse.

Profound shock was present in most cases of spontaneous rupture of the liver and was frequently accompanied by extensive blood loss. However, the premature appearance of such intense prostration suggests an additional etiological factor of neurovascular origin. Certainly, in our patient, this rapid deterioration, in the presence of unchanged hemoglobin and hematocrit levels, tended to obscure the diagnosis.

The most important factor, however, in the diagnosis of spontaneous rupture of the liver is an awareness of the possibility of this occurrence. The difficulty of clinical diagnosis is attested to by the fact that none of the cases reported in the literature was diagnosed prior to operation or autopsy. In each of the cases there were prodromal symptoms and signs related to pre-eclampsia, including headache, vomiting, blurring of vision, albuminuria, and hypertension, and some degree of abdominal discomfort ranging from vague epigastric pain to acute right upper quadrant crisis. In the case of a pregnant multipara with this picture, who progresses to rapid peripherovascular collapse, usually with signs of intraperitoneal hemorrhage, the diagnosis of spontaneous rupture of the liver must be considered.

The only reported survivors of spontaneous rupture of the liver in pregnancy were those who underwent surgical intervention. In each case the preoperative diagnosis was intra-abdominal hemorrhage from a ruptured uterus or abruptio placentae.

The general approach to surgical therapy must include combating the shock, preferably before operative treatment is instituted. However, in considering our case, it is apparent that, since factors other than blood loss may be involved in the shock, this may not be

feasible. An operation may have to be performed despite the extremely poor condition of the patient. There is considerable doubt however that an operation would have been lifesaving in several of the reported cases including our own.

Once the abdomen is opened, partial immediate control of bleeding can be accomplished by digital pressure of the portal vein and hepatic artery in the region of the foramen of Winslow. More permanent measures rapidly should be undertaken, and Kramish<sup>15</sup> outlines the following methods: (1) packing with various materials: Gelfoam, Oxycel, gauze, fat, and muscle; (2) suture of the laceration by the use of a blunt noncutting needle and the ligation of the bleeding point with either absorbable or nonabsorbable material; (3) electrocoagulation by the use of cautery; and (4) compression clamps.

Following operation an adequate evaluation of the patient's pre-eclamptic state should be made with determination of the physiologic status of the liver and kidney.

### Summary

1. A case of spontaneous rupture of the liver in pregnancy is presented which followed the general pattern of age, multiparity, coexistent hypertension, location of lesion, grave prognosis, and failure of diagnosis before autopsy.

2. A review of the literature makes it apparent that the crux of diagnosis is an awareness of this entity which has a rather characteristic clinical picture of a patient in advanced pregnancy complicated by toxemia and right upper quadrant pain, who rather rapidly develops shock. Evidence of intraperitoneal hemorrhage and signs of blood loss may not be present.

3. The profound collapse present in our patient suggested that a neurovascular mechanism was combined with a relatively mild hypovolemia as an etiological factor.

4. If the occurrence of irreversible shock can be forestalled by immediate resuscitative measures, operation should be successful in avoiding fatalities.

### REFERENCES

1. Abercrombie, J.: *London M. Gazette* 34: 792, 1844. (Quoted by Rademaker.<sup>8</sup>)
2. Kosoloff: Cited by Herz.<sup>3</sup>
3. Herz, A.: *Zentralbl. Gynäk.* 42: 572, 1918. (Quoted by Rademaker.<sup>8</sup>)
4. Kolisko, A.: Cited by Speert and Tillman.<sup>14</sup>
5. Duverges, C. J.: *Semana méd.* 35: 1267, 1928. (Quoted by Rademaker.<sup>8</sup>)
6. Roblee, M.: Cited by Dieckmann, W. J.: *The Toxemias of Pregnancy*, St. Louis, 1941, The C. V. Mosby Company.
7. Roemer, H., Jr.: *Zentralbl. Gynäk.* 65: 383, 1941. (Cited by Haller.<sup>13</sup>)
8. Rademaker, L.: *Ann. Surg.* 118: 396, 1943.
9. Lascarro, J., and Gonzalez-Warcalde, J.: *Obst. y ginec. latino-am.* 2: 757, 1944. (Quoted by Howard and Fandrich.<sup>16</sup>)
10. Sanes, S., and Kaminski, C. A.: *AM. J. OBST. & GYNEC.* 52: 325, 1946.
11. Links, H.: *Brit. M. J.* 1: 275, 1946.
12. Burton-Brown, J. R. C., and Shephard, J. A.: *Brit. M. J.* 1: 941, 1949.
13. Haller, A. P., Abels, D. W., and Straus, R.: *AM. J. OBST. & GYNEC.* 62: 1170, 1951.
14. Speert, H., and Tillman, A. J. B.: *AM. J. OBST. & GYNEC.* 63: 1127, 1952.
15. Kramish, D., Auer, E. S., and Reckler, S. M.: *Obst. & Gynec.* 4: 21, 1954.
16. Howard, P. J., and Fandrich, T. S.: *Obst. & Gynec.* 7: 40, 1956.
17. Pereyra, A. J., and Lawler, M. P.: *Obst. & Gynec.* 7: 552, 1956.
18. Fazekas, I. G., and Jakobovits, A.: *Gynaecologia* 143: 38, 1957.
19. Cerone, D. M., and Catalino, G.: *Obst. & Gynec.* 12: 459, 1958.
20. Alons, F.: *Nederl. tijdschr. geneesk.* 102: 37, 1958.
21. Devic, E., and Beriel, L.: *Ann. dermat. et syph.* 7: 642, 1906. (Cited by Burton-Brown and Shephard.<sup>12</sup>)
22. Eames, D. H. Jr.: *AM. J. OBST. & GYNEC.* 67: 1358, 1954.
23. Ridley, D. S.: *J. Path. & Bact.* 63: 17, 1951.
24. Best, C. H., and Taylor, N. B.: *The Physiological Basis of Medical Practice*, Baltimore, Md., 1950, Williams & Wilkins Company, p. 359.
25. Howard, B. K., Goodson, J. H., and Mengert, W. F.: *Obst. & Gynec.* 1: 371, 1953.
26. Schweinburg, F. B., Shapiro, P. B., Frank, E. D., and Fine, J.: *Proc. Soc. Exper. Biol. & Med.* 95: 646, 1957.
27. Zweifach, B. W., Benacerraf, B., and Thomas, L.: *J. Exper. Med.* 106: 403, 1957.

# Purpura fulminans complicating pregnancy

R. H. SEINFELD, M.D.

G. HENNIGAR, M.D.

L. M. HELLMAN, M.D.

Brooklyn, New York

WHEREAS idiopathic thrombocytopenic purpura is rare in pregnancy, reports of fulminating nonthrombocytopenic purpura, purpura fulminans, during the course of gestation are virtually nonexistent. The latter is an acute, rapidly progressive and frequently fatal type of purpura, occurring most often in association with acute infectious processes. The platelets are normal, and the cause of the disease is unknown. It was first described by Guelliot<sup>21</sup> in 1884, and again by Henoch<sup>22</sup> in 1887, who reported 4 cases of this disease.

Osler's classic description of the disease in 1908 has hardly been improved upon in over 50 years. He states, "In this rare variety [of purpura] ecchymoses extend with startling rapidity, and within a few hours an entire extremity or the greater part of the trunk may assume a blue or reddish-black color. The disease usually ends fatally in from 18 to 48 hours, and no patient has recovered."<sup>1</sup>

Tinsley Harrison, in *Principles of Internal Medicine* devotes only 5 lines to purpura fulminans which he notes to be "a very rare form of nonthrombocytopenic purpura which affects children chiefly and is characterized by sudden onset, fever, symmetric ecchymoses in the skin without hemorrhage from the mucous membranes, and a fatal course of 1 to 4 days."<sup>11</sup>

Most of the reported cases of purpura fulminans follow acute infectious disease, principally scarlet fever.

*From the State University of New York, College of Medicine at New York City and The Kings County Hospital, Brooklyn.*

*Presented at a meeting of the Brooklyn Gynecological Society, May 20, 1959.*

Bertling, in 1909, reported a case in an 18-year-old man with scarlet fever, with death ensuing in 17 hours.<sup>2</sup>

Biernacki,<sup>3</sup> in 1913, presented a fatal case in a 6-year-old boy following scarlet fever. The white blood count in this case rose to 50,000 with a predominance of polymorphonuclear leukocytes. McConnell,<sup>4</sup> in 1922, reported a case in a 6-year-old girl on the fifteenth day after scarlet fever. He described multiple ecchymoses involving extremities, the nose, buttocks, and back with a temperature rise to 105.8 degrees. Death occurred 4 days after the onset of the purpuric rash. Microscopic examination of skin sections showed the lesion to be due to rupture of blood vessels following thrombosis of these vessels after injury to their walls.

Fox and Enzer,<sup>8</sup> in 1938, published 4 cases of purpura following scarlet fever with no unusual hematologic changes. "Prominent" was the absence of any enlargement of liver or spleen. The confluent appearance of the rapidly spreading lesions was also a prominent feature in their cases.

Chambers, Holyoke, and Wilson,<sup>15</sup> in 1952, discussed 2 cases of fulminating subcutaneous hemorrhages with death following scarlet fever. Laboratory findings were equivocal.

Taylor and Wright,<sup>19</sup> in 1956, stated that nonthrombocytopenic cutaneous purpura with a tendency toward gangrenous changes was not uncommon in the course of meningococcal septicemia and beta-hemolytic streptococcal infections, over 100 cases being described in the literature. They reported 2 additional cases, with pain as an important feature; both patients recovered.



Up to the time Rushmore<sup>5</sup> described a patient with purpura fulminans complicating pregnancy, there was no attempt to differentiate between those purpuras associated with defects in the clotting mechanism and those in which no defect was demonstrable. In 1925, at a meeting of the American Gynecological Society in Washington, D. C., he presented one case of his own of pregnancy complicated by fulminating purpura. The purpura was limited to the skin and was accompanied by severe pruritus. The patient was a 29-year-old woman in the sixth month of gestation who, 2 weeks after an attack of bronchitis, developed red blotches progressing to large ecchymotic areas covering 25 per cent of her legs, thighs, buttocks, and back. Five days after the ecchymoses appeared, she spontaneously aborted a dead fetus. She then went on to complete recovery.

Included in the report are 47 cases of purpura associated with pregnancy gathered from the literature. Rushmore<sup>5</sup> believed his to be the first of this type of purpura, i.e., the idiopathic, possibly allergic type. The others (33 of which had been previously collected by Ferroni<sup>23</sup> in 1903) were apparently of the thrombocytopenic type. Of these 47 cases, 26 mothers and 27 children died.

More recently, Barnes,<sup>10</sup> Glick,<sup>13</sup> Miner,<sup>18</sup> and Chalmers<sup>17</sup> have reviewed cases of thrombocytopenic purpura in pregnancy. Robson and Davidson,<sup>12</sup> in 1950, summarized all purpuras in pregnancy and attempted to break them down into two groups: thrombocytopenic and nonthrombocytopenic. Of the 95 reported cases, they accepted 21 cases as being due to idiopathic thrombocytopenic purpura, and 24 cases as being due to secondary thrombocytopenia. In only one case, that of Stone and Bunim,<sup>7</sup> was the platelet count normal. The 24 cases all followed infection, toxic agents, or systemic diseases which might produce purpura or cause a diminished platelet count. There can be no doubt, however, that the vast majority of those described are of the thrombocytopenic variety and differ from the case about to be reported not only in this respect but also in the course of the illness.



Fig. 1. Purpuric area on bridge of nose.

Stone and Bunim's<sup>7</sup> patient, in 1936, subsequently died of acute yellow atrophy of the liver. They were able to find only one questionable case in the prior literature of nonthrombocytopenic purpura in pregnancy, that of Wiener<sup>24</sup> in 1887. Their own case was highly debatable in that they felt that the use of intravenous gum acacia glucose in therapy might have been a predisposing factor in the production of the severe facial purpura.

The following case, we feel, is unique and is worthy of report because of the extreme rarity of fulminating nonthrombocytopenic purpura associated with pregnancy.

#### Case report

I. M. was a 28-year-old Puerto Rican, para 2-0-1-2, whose last normal menstrual period was Sept. 7, 1958. She was admitted to the Gynecological Service on Jan. 30, 1959, with fever, chills, and lower abdominal pain of 3 days' duration. Other than taking a Lysol douche one week prior to admission, the patient denied any attempt at intervention with a known pregnancy. She gave no history of previous gynecological disease. Medical, surgical, and family histories were not remarkable. Examination on admission revealed a blood pressure of 110/60, a pulse of 120 beats per minute, respirations of 22 per minute, and a temperature of 104° F. The patient appeared to be in no apparent distress. General physical ex-



amination showed the skin to be completely normal. Examination of the abdomen revealed the uterus to be enlarged to a 20 weeks' gestational size. No fetal heartbeat was elicited. There was minimal left lower quadrant abdominal tenderness. The bowel sounds were normal. The pelvic examination disclosed a patulous, soft, nontender, closed cervix and a uterus which was irregularly enlarged to the size of 20 weeks' gestation. The adnexa were normal. There was no evidence of staining or of bleeding vaginally at any time. The hemoglobin level on admission was 13 Gm. per cent. The urinalysis showed a trace of albumin and a 4-plus acetonuria. There were 5 white cells per high-power field in the urine. The white blood count was 14,000 per cubic millimeter. Because of an initial impression of pyelonephritis of pregnancy, urinary culture and sensitivity tests were taken and the patient was placed on intravenous Achromycin, 500 mg. in 1,000 c.c. of glucose and water. At 2:45 A.M. on January 31, approximately 4 hours after admission to the hospital, the patient was spontaneously delivered of a macerated fetus and a large amount of placental tissue. Following delivery, her temperature rose to 106° F. and no blood pressure could be detected in either arm. The peripheral pulses also became imperceptible. There was no evidence at this time of major blood loss. During the following hours she expelled a satisfactory quantity of clear, yellow urine, but the blood pressure was still unobtainable. At 3:30 A.M. an intravenous infusion containing 10 mg. of Neo-Syneprine was begun with no response. An infusion of metaraminol bitartrate (Aramine), 1 per cent, was then started in the patient's left arm with an immediate response bringing the pressure to 110/60, but this effect lasted for only 20 minutes and the pressure again disappeared. At 7:30 A.M. on Jan-

uary 31 a cut-down with polyethylene catheter was placed in the patient's right arm and an intravenous infusion containing 2 ampules of noradrenaline (Levophed) in 1,000 c.c. of glucose and water, was begun. It was at this time that a purpuric rash was noted on the anterior chest wall, lower abdomen, left arm, right arm, and right ankle. Despite the difficulties with pressure and pulse during the first night, the patient's urinary output was 400 c.c. of clear, yellow urine with specific gravity of 1.017 (Figs. 1-4).

On January 31 the purpuric areas widened considerably and became noticeably confluent. The blood pressure and pulse remained imperceptible throughout the entire day. On the evening of January 31, the Levophed solution was increased in concentration to 4 ampules per 1,000 c.c. of glucose and water. The urinary output continued to remain satisfactory and the fluid intake was balanced according to the output. The temperature, which had been 106° F. at the time of delivery, rapidly fell on the morning of January 31 to 98° F. By midmorning, a purpuric rash was noted appearing on the bridge of the patient's nose. Blood studies carried out at this time revealed a hemoglobin level of 13 Gm. per cent, a hematocrit level of 40 per cent, a sedimentation rate of 10 mm. per hour, and a white blood count of 4,000 per cubic millimeter with a predominantly polymorphonuclear leukocyte count. There was a shift to the left with no very early forms reported. The bleeding time was 4 minutes and the clotting time was 3 minutes. Smears taken by the Hematological Service were reported to have a normal number of platelets. Clot retraction also was normal. By the evening of January 31, the left arm was completely discolored from the tips of the fingers up to the elbow. The forearm was markedly edematous and cold, but sensation remained intact. On the right arm, confluent areas had developed into a patchy, purpuric rash which covered a good portion of the right forearm. At 10 P.M. on January 31, because of a tachycardia of 140 beats per minute, the patient was given digitalis rapidly. Solu-Cortef, 100 mg., was administered intravenously.

The patient was started on 30 million units of penicillin a day intravenously as well as 1 Gm. of streptomycin twice a day intramuscularly. In addition to the penicillin and streptomycin, the patient was also started on Chloromycetin, 1 Gm. per day intravenously.

On February 1, the patient appeared to be improved. A palpable pulse and an audible pres-

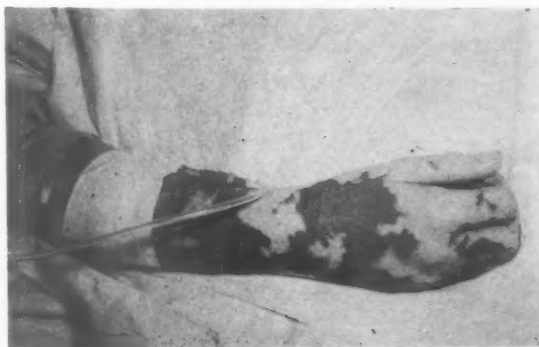


Fig. 2. Patchy purpuric rash on right forearm.

sure were obtained at approximately 90 systolic and 60 diastolic. The urinary output continued to maintain itself satisfactorily. The purpuric areas on the chest appeared to recede somewhat although the hemorrhagic areas on the arms and nose and right ankle did not change in appearance. At this time the patient began to complain of abdominal pain, but examination did not reveal any enlargement of the liver or spleen, and the abdomen remained soft. A white blood count on February 1 was 64,000 with a shift to the left and no early forms reported. Blood chemical determinations were as follows: blood urea nitrogen, 51 mg. per cent as compared to 37 mg. per cent on the morning of admission; carbon dioxide combining power, 10.2 millimols per liter; and chlorides, 90 mEq. per liter. On February 2, deterioration and mental confusion were apparent. The blood urea nitrogen rose to 61 mg. per cent. The carbon dioxide combining power remained at 10.2 millimols per liter and the chlorides were 87 mEq. per liter. A white blood count on this date was 77,000. Hemoglobin and hematocrit remained essentially unchanged. During this day abdominal tenderness was elicited and bowel sounds became hypoactive. Re-examination of the chest revealed no evidence of fluid accumulation. On the evening of February 2 the BUN had risen to 71 mg. per cent, but the white blood count had fallen to 44,000. Carbon dioxide combining power was now 13.4 millimols per liter; chlorides, 100 mEq. per liter; and sodium, 121 mEq. per liter. X-ray plates of both abdomen and chest were not remarkable. Electrocardiograms revealed only a sinus tachycardia. On February 3, deterioration continued. No further purpuric areas appeared anywhere on the body, but during this

day the patient appeared to be in some respiratory distress. The chest, however, remained clear to percussion and auscultation. Blood pressure was now being maintained, without the aid of hypertensive agents, at 100/60, and the urinary output remained satisfactory. The specific gravity of the urine on this day was 1.010. The serum potassium level was reported as 4.9 mEq. per liter on February 3. Hematemesis had been noted on February 1 and February 2. At no time was there any rectal bleeding. On February 3, blood cultures, urine cultures, and uterine cultures were reported as being negative. At 4:20 A.M. on February 4, the patient died.

*Postmortem findings.* Purpuric areas were present over the bridge of the nose and lower extremities. Diffuse purpura was noted over both forearms. The underlying subcutaneous tissue was edematous, hemorrhagic, and, in some areas, necrotic. The pleural and abdominal viscera were not remarkable with the exception of some slight pulmonary edema and congestion. There was no evidence of gastrointestinal hemorrhage. Multiple coronal sections of the brain revealed no purpuric or hemorrhagic lesions.

The uterus was slightly enlarged and contained some membranes in its cavity. There was no evidence of infection or traumatic perforation. One ovary presented a corpus luteum of pregnancy.

The anatomical diagnoses were (1) diffuse vascular purpura dermis, (2) pulmonary edema and congestion, and (3) postabortive uterus.

The histologic findings of interest were confined to the dermis and subcutaneous tissue. The changes consisted of fibrinoid necrosis of small capillaries and occasional venules, with thrombosis and perivascular hemorrhage which sometimes



Fig. 3. Appearance of left arm on Jan. 31, 1959.



Fig. 4. Resolution of lesions of lower extremities.

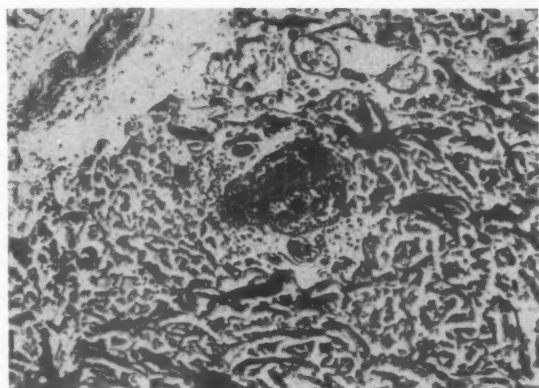


Fig. 5. Dermis with fibrinoid necrosis, thrombosis, and perivascular hemorrhage of dilated vessel. (Hematoxylin and eosin.  $\times 60$ ; reduced  $\frac{2}{3}$ .)

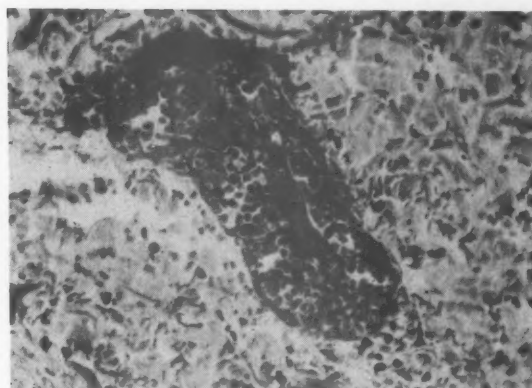


Fig. 6. Dilated capillary with fibrinoid necrosis at one pole. Perivascular infiltrate scanty. (Hematoxylin and eosin.  $\times 250$ ; reduced  $\frac{2}{3}$ .)

was extensive. The inflammatory component consisted of neutrophilic polymorphonuclear leukocytes in the walls of the vessels; eosinophils were conspicuous by their absence (Figs. 5 and 6).

A careful search failed to reveal any lesions involving the glomerular capillaries or other vascular structures in the body. Minute foci of necrosis were seen here and there in the periportal areas of the liver. No hemorrhagic phenomena in the visceral organs were present.

#### Comment

Fox and Enzer,<sup>8</sup> in 1938, reporting 4 cases of fulminating purpura, noted that snake venom might be indicated to inhibit what they felt was the Schwartzman reaction. Gairdner<sup>9</sup> suggested, in 1948, that purpura fulminans was a variant of Henoch's purpura or anaphylactic purpura, with the Henoch syndrome adding gastrointestinal and joint symptoms, plus nephritis, in addition to the typical skin eruptions described by Henoch in 1887. Taylor and Wright<sup>19</sup> also noted the close similarity of purpura gangrenosa to the Schwartzman phenomenon.

Shwartzman,<sup>6</sup> in 1928, described the phenomenon of local skin reaction to *Bacillus typhosus* culture filtrates caused by skin injections followed 24 hours later by an intravenous injection of the same filtrate, this local reaction being a severe hemorrhagic necrosis 4 to 5 hours after the second injection. The mechanism of this reaction was not determined, but local injections repeated in

the same area did not cause it to occur.

In January, 1959, Little<sup>20</sup> suggested that the term "purpura" was not applicable in purpura fulminans as this disease represented a hypercoagulable state. He stressed again the similarity between purpura fulminans and the Schwartzman reaction. On the basis of the work of Cluff and Berthrong,<sup>16</sup> in 1953, and Good,<sup>14</sup> in 1952, who showed that heparin inhibited the local skin response (i.e., the platelet-leukocyte-thrombi, edema, hemorrhage, and subsequent necrosis), Little successfully treated a 14-year-old girl suffering from purpura fulminans, with heparin.

We would propose that in view of the symptomatology of our case, i.e., purpura, abdominal pains, and hematemesis, as suggested by Gairdner, nonthrombocytopenic purpura fulminans is a variant of allergic purpura. In any event, such a syndrome associated with pregnancy is of extreme rarity, there being only 2 previously reported cases.

#### Conclusion

The specific etiology of the fulminating purpura in our patient is not known; however, she did exhibit the classic signs and course of previously described cases of purpura fulminans. Not only were there extensive areas of skin necrosis and multiple sites of thrombosis, but also severe abdominal symptoms. She had no clotting defect and the course of the disease was rapidly fatal.



## REFERENCES

1. Osler, William: *Osler's Modern Medicine*, Philadelphia and New York, 1908, Lea & Febiger, vol. 4, p. 711.
2. Bertling, F. E.: *J. A. M. A.* 53: 383, 1909.
3. Biernacki, J., and Dykes, A. L.: *British M. J.* 2: 903, 1913.
4. McConnell, G., and Weaver, H. L.: *J. A. M. A.* 78: 165, 1922.
5. Rushmore, S.: *AM. J. OBST. & GYNEC.* 10: 553, 1925.
6. Schwartzman, G.: *J. Exper. Med.* 48: 247, 1928.
7. Stone, M. L., and Bunim, J. J.: *AM. J. OBST. & GYNEC.* 31: 1015, 1936.
8. Fox, M. J., and Enzer, N.: *Am. J. M. Sc.* 196: 321, 1938.
9. Gairdner, D.: *Quart. J. Med.* 17: 95, 1948.
10. Barnes, A. C., and Doan, C. A.: *AM. J. OBST. & GYNEC.* 55: 864, 1948.
11. Harrison, T. R., et al.: *Principles of Internal Medicine*, New York, 1950, Blakiston Company.
12. Robson, H. N., and Davidson, L. S. P.: *Lancet* 2: 164, 1950.
13. Glick, L. J., and Weisner, N. J.: *J. A. M. A.* 147: 44, 1951.
14. Good, R. A., and Thomas, L.: *J. Lab. & Clin. Med.* 40: 804, 1952.
15. Chambers, W. N., Holyoke, J. B., and Wilson, R. F.: *New England J. Med.* 247: 933, 1952.
16. Cluff, L. E., and Berthrong, M.: *Bull. Johns Hopkins Hosp.* 92: 353, 1953.
17. Chalmers, J. A.: *J. Obst. & Gynaec. Brit. Emp.* 61: 675, 1954.
18. Miner, P. F., Nutt, R. L., and Thomas, M. E.: *AM. J. OBST. & GYNEC.* 70: 611, 1955.
19. Taylor, K. B., and Wright, F. W.: *Lancet* 2: 284, 1956.
20. Little, J. Russell: *J. A. M. A.* 169: 36, 1959.
21. Guelliot, A.: *Union méd du nord-est* 8: 25, 1884.
22. Henoch, Eduard: *Berl. klin. Wchnschr.* 24: 8, 1887.
23. Ferroni, E.: *Ann. di ostet. e ginec.* 25: 30, 1903.
24. Wiener, M.: *Arch. f. Gynäk.* 31: 281, 1887.



## Pregnancy and delivery following extensive vulvectomy

JASON H. COLLINS, M.D.  
HERBERT W. BIRCH, M.D.  
MAX PAILET, M.D.  
JAMES K. AVENT, M.D.  
*New Orleans, Louisiana*

DURING the period Jan. 1, 1946, to Jan. 1, 1959, 128 extensive vulvectomies were performed by the staff, residents, and Fellows of the Department of Obstetrics and Gynecology, Tulane University of New Orleans. Most of these were from the Tulane Unit of Charity Hospital but some were performed in private practice by the senior author. Extensive vulvectomy was performed in 76 instances for malignancy. Twelve of these were preinvasive. The 64 patients with invasive malignancy were also treated by bilateral lymphadenectomy plus partial or total exenteration in 7 cases. In 52 patients, vulvectomy was done for benign disease (Table I). Our indications for vulvectomy in benign disease are listed elsewhere.<sup>1</sup> The scope and technique of the procedure are essentially the same for benign and malignant disease and are also described in a previous communication.<sup>1</sup> Our method of extensive vulvectomy (classed as radical vulvectomy at many centers) is rapid, safe, and dry and has resulted in primary healing in 85 per cent of cases. The patients are comfortable and can care for themselves by 24 hours

post operation. Most of them go home in 7 to 10 days.

Inasmuch as a number of our patients were young women, we became interested in the effect of the operative procedure upon the sexual activity of the patients. This was investigated and several interesting factors have been revealed:

1. All of the patients who were interested in intercourse prior to the operation were able to fulfill these desires after healing.

2. Those patients who were able to attain orgasm during intercourse before the procedures were performed were able to do so after.

It is not surprising then, that of 27 patients who were operated upon and who were capable of conceiving, 7 became pregnant. These 7 women were delivered of a total of 11 babies following extensive vulvectomy (Table II).

In a careful review of the literature, we were able to find reports of 7 other women who had vulvectomy and who were subsequently delivered (Table III). Heinman,<sup>2</sup> in 1931, reported the case of a 27-year-old woman who was delivered vaginally 6 and 9 years after radical vulvectomy for cancer. Russell,<sup>3</sup> in 1940, described a squamous carcinoma of the vulva in a 19-year-old Negro at 7 months' gestation which was treated by "radical vulvectomy." She was delivered at term by elective cesarean section and the

*From the Department of Obstetrics and Gynecology, Tulane University School of Medicine, and the Division of Obstetrics and Gynecology, Tulane Unit, Charity Hospital of Louisiana in New Orleans.*

*Aided by the Ex-Residents and Fellows Research Fund.*

**Table I.** Vulvectomies from Jan. 1, 1946, to Jan. 1, 1959

For malignant disease	76
Preinvasive	12
Invasive	64
For benign disease	52
Total	128

**Table II.** Vulvectomies and pregnancies Jan. 1, 1946, to Jan. 1, 1959

Extensive vulvectomies	128
Capable of pregnancy	27
Patients becoming pregnant	7
Babies delivered	11

nodes were treated by radium and deep x-ray. Shannon and Marting,<sup>4</sup> in 1941, published a case of a 26-year-old white woman, gravida iii, para 0, at 6½ months' gestation who had a squamous carcinoma which was 6 cm. in diameter. She received only simple vulvectomy and was delivered at 8 months by elective cesarean section. The male infant weighed 6 pounds, 3 ounces. Bilateral lymphadenectomy was done 4 months later and was followed by deep roentgen therapy to the pelvis. Lunin,<sup>5</sup> in 1949, mentioned a patient who was delivered shortly after vulvectomy and who had a subsequent pregnancy 4 years later. We do not know how this woman was delivered. Way<sup>6</sup> told of a 25-year-old patient on whom

he had operated for carcinoma of the vulva and who delivered 2 and 5 years later by elective cesarean section. He also mentions the experience of Haultain who encountered a case necessitating cesarean section following vulvectomy for cancer. Then, more recently, Rubin and Lewis,<sup>7</sup> in 1953, reported a case of a 37-year-old patient who had vulvectomy and bilateral lymphadenectomy for carcinoma. The nodes were negative. Fifteen months later she was delivered vaginally without episiotomy under general anesthesia. The infant was premature and there were no lacerations of the maternal tissues. The woman was well with no recurrence 2 years postoperatively. Of these 7 reported cases, there were 10 babies. Five were delivered by cesarean section, 3 were delivered vaginally, and we do not know about the other 2 (Table III). Thus, we see that of 8 previously delivered babies, 5 were managed by cesarean section. The purpose of this paper is to show that the patient who has had a vulvectomy does not necessarily require cesarean section for her subsequent deliveries.

### Material

The 7 patients comprising the basis for this report were all managed by the same team and therefore reflect results obtainable by a unified operative technique. There were 27 patients theoretically capable of

**Table III.** Previous reports

Author	Date	Vulvar lesion	Procedures	Age of patient	Interval operation to delivery	Mode of delivery
Heinman <sup>2</sup>	1931	Cancer	Radical vulvectomy	27	6 years	Vaginally
Russell <sup>3</sup>	1940	Squamous carcinoma	Radical vulvectomy (radiation to pelvic nodes post partum)	19	9 years	Vaginally
Shannon and Marting <sup>4</sup>	1941	Squamous carcinoma	Simple vulvectomy (bilateral lymphadenectomy plus deep x-ray 4 months post partum)	26	2 months	Cesarean
Lunin <sup>5</sup>	1949	Carcinoma	Radical vulvectomy	26	6 weeks	Cesarean
Way <sup>6</sup>	1951	Carcinoma	Radical vulvectomy	29	?	?
Haultain <sup>6</sup>					4 years	?
Rubin and Lewis <sup>7</sup>	1953	Cancer	Radical vulvectomy	25	2 years	Cesarean
		Squamous carcinoma	Radical vulvectomy		5 years	Cesarean
			Bilateral lymphadenectomy	?	?	Cesarean
				37	15 months	Vaginally

Table IV. Present report\*

Case No.	Age	Parity	Vulvar lesion	Interval operation to delivery (months)	Duration of labor (hours)	Mode of delivery	Anesthesia	Birth weight (grams)
1	35	0	Carcinoma of clitoris 5 cm.	24	0	Cesarean	Spinal	3,500
2	40	2	Chronic atrophic vulvitis	24	2	Low forceps, episiotomy	General	4,300
3	25	3	Lymphogranuloma venereum	24	5	Normal spontaneous	None	3,600
					4	Normal spontaneous	None	1,820
					6	Normal spontaneous	None	4,100
					1	Normal spontaneous	General	4,300
					15	Low forceps	General	3,100
4	18	0	Myoblastoma 6 cm.	18	9	Normal spontaneous LML episiotomy	General	2,500
5	38	0	Fibroma 8 cm.	4	11	Forceps rotation	General	2,600
						Low forceps, episiotomy		
6	19	4	Granuloma inguinale	9	2½	Low forceps, episiotomy	Spinal	3,650
7	28	6	Squamous carcinoma labium 3 cm.	2	4	Low forceps, episiotomy	Spinal	2,500

\*Extensive vulvectomy was used in all cases and additional bilateral lymphadenectomy in Cases 1 and 7.

becoming pregnant following vulvectomy although some of these had known tubal inflammatory disease. Seven became pregnant and/or were delivered of 11 babies after extensive vulvectomy was performed (Table II). Two of the 7 were white and 5 were Negroes. This is in keeping with the racial ratio of operated patients capable of pregnancy. One patient was delivered 5 times and the remaining 6 each accounted for one delivery after vulvectomy. The average age of the patients in the group was 29 years. The oldest person was 40 at the time of operation, and she was delivered at age 42. The youngest was 18 at the time of vulvectomy and 19 when she was delivered.

#### Indications and surgical procedures

The lesions necessitating vulvectomy in 2 instances were squamous carcinoma. In Case 1 (Table IV) the lesion was 5 cm. in diameter arising from the clitoris. The surgical management consisted of extensive vulvectomy and bilateral inguinal and pelvic lymphadenectomy. These were performed in 3 stages approximately one week apart. We consider it necessary to remove the superficial and deep inguinal, Cloquet's, the femoral, the external and common iliac

as well as the obturator, hypogastric, and lower caval and aortic nodes in the therapy of invasive malignancies of the vulva.<sup>8,9</sup> In Case 1, there were one or more positive nodes from each of the aforementioned major groups. This patient was delivered by cesarean section at term 2 years later. Cesarean section was chosen to allow careful palpation and observation for possible persistence of tumor within the pelvis; none was found. She is alive and well with no evidence of recurrence of the disease 11 years following operation. The other patient with carcinoma (Case 7, Table IV) was pregnant and at 6½ months' gestation when she registered in the clinic, and a 2 cm. lesion was discovered on the left labium minus. Extensive vulvectomy was performed one week later and she was delivered vaginally at term. Bilateral lymphadenectomy was performed 2 weeks following vulvectomy and there were no positive nodes. Benign tumors prompted vulvectomy for 2 patients (Cases 3 and 4, Table IV). One was a myoblastoma and the other a large degenerating fibroma. There were 3 patients with chronic vulvitis and all of these were symptomatic for 3 or more years despite repeated attempts at medical control. Two

had hypertrophic vulvar tissues following granulomatous venereal diseases. Extensive vulvectomy was utilized in all 7 of these patients and all remain asymptomatic with no return of the original lesions.

#### **Gravidity and parity**

Three of the patients were nulliparous (Table IV) although one had had a previous spontaneous early abortion. The 4 multiparous patients had 19 previous pregnancies with 4 ending in spontaneous abortion and one an ectopic pregnancy. Following vulvectomy there were no abortions but one patient was delivered of a premature infant (Case 3, Delivery B, Table IV) at 32 weeks. The baby survived and was discharged from the hospital in good condition 12 weeks later.

#### **Interval from operation to delivery**

The time interval from operative procedure to the first delivery varied from 2 months to 24 months with an average of 15 months (Table IV). The average interval of all previously reported cases is about 36 months (Table III). In 3 of the formerly recorded cases the patients were known to be pregnant and in the last trimester. Only 2 of the vulvectomies were performed on known pregnant patients and in neither was there any difficulty at the time of operation of increased bleeding or of poor wound healing. There were no apparent ill effects to the maintenance of the pregnancies or to the babies.

The other 9 pregnancies were all subsequent to vulvectomy and all were uneventful. These patients were managed as any other pregnant woman would be and no complications were noted in their antenatal periods.

#### **Labor and delivery**

The duration of labor varied from one hour to 15 hours and the average total labor was 6 hours (Table IV). This certainly does not indicate any prolongation of labor due to scarring of the soft tissues of the perineum. Three labors were less than

3 hours in duration but there was no injury to any of the babies due to birth trauma. We wish to reiterate; in our experience previous vulvectomy does not constitute an indication for abdominal delivery. In fact, only one of our patients was so delivered (Case 1, Table IV). The reason for this, as mentioned before, was to allow investigation of possible persistent metastatic tumor. The others were all delivered vaginally without difficulty. One patient (Case 3, Table IV) was delivered vaginally 3 times, spontaneously, without episiotomy or anesthesia, and without lacerations. Her remaining 2 deliveries were under general anesthesia and in one of her deliveries, low forceps were used. The ideal delivery for these patients is low forceps and episiotomy. No special anesthesia is necessary. Table IV shows that there were 3 deliveries accomplished without anesthesia in the series and that spinal anesthesia was used in 3 cases. The weight at birth varied from 1,820 to 4,300 grams. The 2 patients with 4,300 gram babies were multiparas and, following short labors, were delivered without difficulty (Table IV).

#### **Comment**

Extensive (radical) vulvectomy as performed on the Tulane Service has been shown to be safe, dry, rapid, and associated with minimal complications. Our experience has shown it to be of considerable value in the treatment of both malignant and benign disease. We do not consider vulvectomy to be a mutilating operation either cosmetically or functionally. Practically all women are able to continue in whatever sexual pattern they had previously established. In this group of 7 women, 6 experience orgasm. One who does not failed to do so prior to the procedure. In addition, intercourse is now contraindicated for her husband because of repeated coronary artery occlusions. These 7 women conceived one or more times and all but one of the 11 babies were carried uneventfully to term. The one premature infant was delivered at 7½ months' gestation and did well. In none



of these patients was there any excessive scar formation or soft tissue contracture following extensive vulvectomy. All of these babies were delivered vaginally except one and there were no difficulties of labor or delivery. Cesarean section need be resorted to only for the usual obstetrical indications.

### Conclusions

1. One hundred twenty-eight extensive vulvectomies have been performed for ma-

lignant and benign disease of the vulva. Of 27 patients capable of conceiving, 7 became pregnant and were delivered of a total of 11 babies.

2. These pregnancies resulted in uneventful antepartal courses. The labors and vaginal deliveries were uncomplicated. The method of choice for delivery is low forceps and episiotomy.

3. Extensive vulvectomy, as performed at Tulane, apparently does not disturb sexual life or childbearing function.

---

### REFERENCES

1. Collins, G. G., Burman, R. G., McMahon, D., and Avent, J. K.: *AM. J. OBST. & GYNEC.* 76: 363, 1958.
2. Heinman, F.: *Zentralbl. Gynäk.* 55: 2869, 1931.
3. Russell, P. B.: *AM. J. OBST. & GYNEC.* 39: 873, 1940.
4. Shannon, W. F., and Marting, E.: *AM. J. OBST. & GYNEC.* 41: 117, 1941.
5. Lunin, A. B.: *AM. J. OBST. & GYNEC.* 57: 742, 1949.
6. Way, S.: *Malignant Disease of the Female Genital Tract*, Philadelphia 1951, Blakiston Company.
7. Rubin, A., and Lewis, G. C.: *AM. J. OBST. & GYNEC.* 65: 1347, 1953.
8. Collins, C. G., Collins, J. H., Nelson, E. W., Smith, R. C., and MacCallum, E. A.: *AM. J. OBST. & GYNEC.* 62: 1198, 1951.
9. Collins, C. G., Collins, J. H., Cassidy, R. E., and Burman, R. G.: *Dallas M. J.* 43: 675, 1957.

# Intestinal obstruction associated with pouches and fenestrae in the broad ligament

Review of the literature and report of a case

HARRY N. PAPAS, M.D.

Akron, Ohio

INTESTINAL obstruction based on broad ligament fenestrae seems to be extremely rare, even when compared with the uncommon forms of intestinal strangulations into other peritoneal fossae and apertures. Early in 1889, Dulles<sup>4</sup> collected more than 70 cases of properitoneal hernia, and Moynihan,<sup>9</sup> in 1906, reported 81 cases of hernia into the duodenal fossae, while Judd,<sup>8</sup> in 1929, found 29 cases of strangulations through holes of the mesentery.

However, there have been reported in the literature only 44 cases of intestinal obstruction following protrusions and strangulations of loops of bowel through defects in the broad ligaments. In addition to these, 4 cases of defects in the broad ligament unassociated with strangulation have been described. Herrmann,<sup>6</sup> in 1925, reported one in a nulliparous girl of 18 years in whom bilateral pouches were discovered during the removal of an ovarian tumor. The second case of the 4, was that of Pemberton and Sager,<sup>12</sup> who found bilateral holes at the points where the round ligament was brought through the broad ligament in a Baldy-Webster operation. Masson and Atkinson<sup>10</sup> reported, in 1934, a case of herniation of the right ovary and part of the Fallopian tube into a fold of the right broad

ligament, giving the picture of an acute condition of the abdomen. Our case, here presented, is the fiftieth.

## Historical

Before the twentieth century the first who mentioned such a condition was Quain,<sup>14</sup> in 1861, who found it at an autopsy in a 36-year-old woman who was admitted with a sudden, sharp pain in the lower abdomen and who died 3 days after the onset of the pain without being operated upon. At autopsy he found that the bowel was incarcerated in two places on the right side of the pelvis; at one by old adhesions between the broad ligament and the mesentery and at the other by an aperture in the right broad ligament.

Treves,<sup>15</sup> in 1885, made a thorough description of "hernias" of the intestines and peritoneum, but he did not mention broad ligament malformations as being responsible for intestinal obstruction. Likewise, Moynihan,<sup>9</sup> in 1906, and Watchon do not refer to this condition.

Barnard,<sup>1</sup> in 1910, mentioned that there was a case of hernia in a pouch in the broad ligament in the Museum of the London Hospital, but it was not until 1917, when Fagge<sup>5</sup> reported 2 cases of intestinal obstruction into pouches or through fenestrae of the broad ligament, that surgical treatment was instituted. Richardson,<sup>16</sup> in 1920, reported the first instance of intestinal obstruction following and definitely associated with the Baldy-Webster operation.

*From the Department of Obstetrics and Gynecology, St. Thomas Hospital*

*Present address: Department of Obstetrics and Gynecology, Akron City Hospital.*

### Anatomical considerations

The broad ligaments are two thin fibrous sheets, covered on both surfaces with peritoneum, which extend from each side of the uterus to the lateral pelvic wall. At the upper end of each lateral margin of the uterus the Fallopian tube pierces the uterine wall. Below and in front of this point, the round ligament of the uterus is fixed, while behind it is the attachment of the ligament of the ovary. On the lateral pelvic wall, behind the attachment of the broad ligament, in the angle between the elevation produced by the diverging of the hypogastric and external iliac vessels, is a slight fossa, the ovarian fossa, in which the ovary normally lies. The ligamentum ovarii proprium extends between the ovary and the cornu of the uterus and divides the broad ligament into two parts: the upper, triangular—the mesosalpinx—with the uterus, Fallopian tube, and ovary, respectively, as boundaries, and the lower, which is bordered by the uterus medially, the ovarian ligament superiorly, the pelvic wall and the suspensory ligament of the ovary laterally.

Hunt,<sup>7</sup> in his review, stated that among 17 cases the incidence of pouches occurred 5 times and the openings 12. Where the location of the openings was mentioned, they were situated above the ligamentum ovarii proprium twice and below once. The pouches always occurred below the ovarian ligament, near the uterus.

### Etiology

The opinion of the writers regarding the cause of the broad ligament defect differs considerably.

Pidcock<sup>13</sup> suggests as a possible cause of the condition, in his case reported in March, 1924, the fact that all structures connected with the uterus were in a relaxed condition as a result of the pregnancy and that a coil of intestine had, in some manner, ruptured the mesoligamentous fold. Dunn,<sup>3</sup> on the other hand, in his review in 1926, stated that in his case it was probable that congenital stomas existed because of the fact that there were, in both broad ligaments,

openings of about the same size which were symmetrical and with smooth edges. No evident previous inflammation was found.

Hunt, in his review, pointed out 3 causative factors: (1) congenital anomalies, (2) internal lacerations as the result of pregnancy or labor, and (3) defects resulting from previous inflammatory processes. On the contrary, Goode and Newbern<sup>11</sup> believed, because of the fact that in only one case did intestinal obstruction occur during or shortly after the termination of pregnancy, that the second factor of Hunt cannot be proved. There is no doubt that pregnancy must play some role, because it was found that all except 4 patients were multiparas (nonpregnant). The same authors state that, in spite of the fact the mesosalpinx is a thin, avascular region of the broad ligament, it is unlikely that stretching or direct pressure by loops of bowel could produce these defects. Trauma by repeated protrusions of loops of intestine into congenital fenestra, however, might produce sufficient inflammation with resultant fibrous tissue strong enough to strangulate the bowel. This causative mechanism for intestinal obstruction requires many years of such repeated mild trauma until the expression of the acute picture.

The Baldy-Webster operation for uterine suspension was, according to Baron,<sup>2</sup> the most frequent predisposing factor. This is due to two things: (1) improper closing of the openings by stitching their edges to the round ligament and (2) drawing the round ligament through the broad ligament too far lateral to the uterus or uteroovarian ligament, thus producing tension on, and later a tear of, the broad ligament.

### Signs and symptoms—diagnosis

Pemberton and Sager made the diagnosis of incarcerated intra-abdominal hernia in a woman who experienced severe colicky-like pain in the lower abdomen 10 days after a Baldy-Webster operation. However, the only suspected intestinal obstruction through a defect of the broad ligament in a patient who had undergone a uterine

suspension 3 years previously, was made by the Italian, Amadei.<sup>17</sup> In none of the other cases reported was the diagnosis made prior to laparotomy. The diagnosis was usually torsion or rupture of an ovarian cyst, strangulated obturator hernia, mesenteric thrombosis, or acute appendicitis.

Sudden, violent, and agonizing abdominal pain followed by nausea and vomiting are the most common symptoms with which this clinical condition begins. Sometimes, straining at stool or any other effort may facilitate the onset of the pain, which may be general throughout the abdomen or more localized to a certain point, according to the location of the lesion. The pain may be cramplike—as in our case—or colicky-like, constant with accentuations at short, irregular intervals.

There are no bowel movements or passage of flatus after the onset of the symptoms. On palpation there is tenderness and sometimes rigidity at the point of the lesion. Sometimes a mass can be palpated in one of the lower quadrants. Rectovaginal examination gives findings such as tenderness, thickening in the lateral fornix, and occasionally a mass, but not always. In nonobstructive herniations of bowels through the broad ligament periodic pains are present which are accentuated by certain movements or positions of the body (pulling of the mesentery). It is worth while to mention here that there is absence of pain during pregnancy because of the closure of the opening as the uterus ascends. Previous history of a uteropexy is very helpful in making the diagnosis.

#### **Treatment—prognosis**

Immediate laparotomy should be performed, and the incarcerated intestine along with obliteration of the pouch or fenestra must be released. Removal of the adnexa may be preferable in an elderly woman or if the circulation is seriously impaired. The mortality rate and prognosis depend on how early the abdominal exploration is instituted.

#### **Case report**

A 34-year-old white woman, gravida iv, para iv, was admitted at St. Thomas Hospital on March 18, 1955, because of a sudden, cramplike pain of 10 hours' duration, which first began in the epigastrium and became localized with persistence in the left lower quadrant, accompanied by nausea and vomiting.

The physical examination showed a well-developed woman acutely ill with the following findings: heart, normal; lungs, clear; abdomen, soft (the patient was given a dose of morphine sulfate) and slightly tender in the left lower quadrant. No masses were palpated. The temperature on admission was 100° F.; pulse, 100; respirations, 20; blood pressure, 110/70. Complete blood count was as follows: packed cell volume, 38; hemoglobin, 76 per cent or 12 Gm.; white blood count, 9,910.

At that time the diagnosis of rupture of a left ovarian cyst was made. The patient had undergone no operations and she had had 4 full-term normal deliveries. A flat plate of the abdomen was taken on admission and revealed a dilated loop of small bowel in the left pelvic region and no urinary stones. A mass was suspected roentgenographically in the left pelvic region, to which a loop of bowel was thought to be adherent.

The patient was taken to the operating room, and a laparotomy was performed. What was thought to be an ovarian cyst on the left side was a loop of small bowel that had entered a small crib and formed a congenital opening in the anterior broad ligament. There was approximately 8 inches of small bowel caught in this opening. The bowel on first inspection, before it was released from the congenital defect in the broad ligament, was purplish in color. Soon after the obstruction was released and the bowel was pulled through the opening, the color improved considerably and, with the application of hot packs, after 30 to 45 minutes, the incarcerated bowel regained its normal color, and there was no area of devitalization. An appendectomy was performed. The opening in the left broad ligament was sutured by a continuous suture of No. 1 chromic catgut. Inspection of the right broad ligament showed an incomplete opening in the same region as on the left; this was closed. The abdominal wall was closed in the usual manner, and the patient was returned to her room in good condition. The postoperative course was uneventful, and she was discharged in good condition 9 days after admission.



### Summary

1. An acute intestinal obstruction through a fenestra of the broad ligament in a woman who had never undergone previous operation is presented.

2. In spite of the rarity of this condition its seriousness necessitates immediate intervention.

3. The etiology of this condition is difficult to determine except in those cases associated with previous uteropexy.

4. In an acute intestinal obstruction, herniation of the bowel through pouches or fenestrae of the broad ligament is one of the possibilities which should be borne in mind, especially in women who have undergone uterine suspension.

My sincere thanks to Dr. C. Paternite, former chief of the Obstetrics-Gynecology Department of St. Thomas Hospital, Akron, Ohio, for permission to present his case.

---

### REFERENCES

1. Barnard, H. L.: Contributions to Abdominal Surgery, London, 1910, Edward Arnold & Company, p. 216.
2. Baron, A.: Brit. J. Surg. 36: 91, 1948.
3. Dunn, L.: Surg. Gynec. & Obst. 42: 398, 1926.
4. Dulles, C. W.: J. A. M. A. 13: 557, 1889.
5. Fagge, C. H.: Brit. J. Surg. 5: 694, 1918.
6. Herrmann, E.: Zentralbl. Gynäk. 49: 63, 1925.
7. Hunt, A. B.: Surg. Gynec. & Obst. 58: 906, 1934.
8. Judd, J. R.: Surg. Gynec. & Obst. 48: 264, 1929.
9. Moynihan, B. G. A.: On Retroperitoneal Hernia, ed. 2, New York, 1906, William Wood & Company.
10. Masson, J. C., and Atkinson, W.: Proc. Staff Meet. Mayo Clin. 8: 293, 1933.
11. Goode, T. V., and Newbern, W. R.: Am. J. Surg. 65: 127, 1944.
12. Pemberton, J. de J., and Sager, W. W.: S. Clin. North America 9: 203, 1929.
13. Pidcock, B. H.: Brit. M. J. 1: 369, 1924.
14. Quain: Tr. Path. Soc. London 12: 103, 1861.
15. Treves, F.: Brit. M. J. 1: 415, 1885.
16. Richardson, E. P.: Surg. Gynec. & Obst. 31: 90, 1920.
17. Amadei, A.: Gior. ital. chir. 2: 261, 1946.

# Chorioadenoma destruens

## A report of 41 cases

H. ACOSTA-SISON, M.D., F.P.C.S.

Manila, Philippines

THIS study is based on 41 cases of chorioadenoma destruens in patients admitted to the Philippine General Hospital between Jan. 1, 1950, and Jan. 9, 1959.

### Pathology and pathogenesis

Following Ewing,<sup>1</sup> the diagnosis of chorioadenoma destruens has been applied to the chorioma which under the microscope reveals one or more chorionic villi amid a group of trophoblasts. Invasive molar cysts seen in the myometrium or in the surrounding structures after the expulsion of an hydatidiform mole are also included in the classification.

Most pathologists regard chorioadenoma destruens to be morphologically benign with hardly any tendency to metastasize and believe that patients harboring it may be cured by simple curettage, provided the growth is confined in the endometrium and that all the chorionic tissue has been removed.

Of the 41 cases of chorioadenoma destruens, 40 were the sequel of hydatidiform mole. One case was preceded by the delivery of a living term baby.

According to Hertig,<sup>2</sup> all cases of chorioadenoma destruens are sequels of hydatidiform moles.

It might be of interest to relate the history of the patient following normal delivery.

The patient was a 25-year-old woman, gravida ii, para ii, who, after the spontaneous delivery of her second baby, menstruated normally for 6 months. She then experienced

irregular, intermittent bleeding and pelvic pain for 3 months, at the end of which time she collapsed. She was taken to a provincial hospital where she was immediately subjected to laparotomy with the preoperative diagnosis of ruptured tubal pregnancy. There was 500 c.c. of intraperitoneal blood, but both tubes and ovaries were normal. The uterus was enlarged to the size of 3 months' pregnancy and was perforated. A subtotal hysterectomy was performed.

Sagittal section of the uterus showed three separate 3 by 3 cm. growths in the myometrium. One of the growths had extended beyond the serosa, giving rise to active bleeding. The endometrium was clean and intact except for a small portion in the neighborhood of one of the growths. A biopsy of the growth was reported

Table I. Complications among 41 cases of chorioadenoma destruens

	No. of cases	Percentage
Perforation of the uterus (in 1 case there were 5 additional intestinal perforations)	10	24
Metastasis	11	27
Total complications	21	51

Table II. Amount of blood in the peritoneal cavity from uterine perforation

Amount of blood (c.c.)	No. of cases
100-300*	4
500	1
1,000	2
1,500	1
2,000	1
Uterine perforation covered by a loop of intestine	1

\*One of these cases showed fecaliths in the peritoneal cavity from multiple intestinal perforations.

From the University of the Philippines.

Table III. Sites of metastases

Site	No. of cases
Generalized (lungs, liver, kidneys, intestines, skin, and brain in conjunction with hydatidiform mole); diagnosed only at autopsy	1
Lungs in conjunction with hydatidiform mole; hysterectomy with the mole in situ; lungs treated by x-ray	2
Lungs and left parametrium; patient died from hemorrhage during surgical removal of parametrial growth	1
Lungs and broad ligaments; treated by x-ray and surgical removal of broad ligament growths	1
Right broad ligament (growth removed surgically)	1
Bilateral parametria (removed surgically)	1
Right parametrium, bladder and upper vagina; died from hemorrhage during operation	1
Mons veneris, left labium majus, and vagina (surgical removal of growths followed by x-ray treatment)	1
Vagina; growths removed surgically	2

by the Laboratory of the Bureau of Hospitals in Manila to show chorioadenoma destruens.

The patient made a smooth postoperative recovery. However, 20 days after the operation she noted vaginal spotting, which gradually increased in amount. At the end of 33 days it was discovered that the bleeding came from a vaginal growth. This was immediately cauterized. The bleeding stopped, only to become more profuse 21 days later. She was taken to the Philippine General Hospital 3 months after the hysterectomy and 70 days after the vaginal metastasis was first noted. She was pale and thin. Examination showed that the bleeding came from a 5 by 2 cm. growth on the right labium majus. The growth extended up into the vagina. At the mons veneris there was a separate 6 by 3 cm. growth beneath the skin. Both growths were removed under spinal anesthesia. The blood loss at operation was copious, but, with the help of blood transfusions and Largactil, the patient survived. The vulva was subjected to x-ray treatments for one week before the frog test of the urine became negative. It is now 4 years since the operation and she is well.

The above case is the only exception to Hertig's dictum that all cases of chorioadenoma destruens result from hydatidiform

mole, unlike choriocarcinoma which may result from any form of pregnancy.

#### Uterine perforation and metastases

Table I shows that, of the 41 patients with chorioadenoma destruens, 21 or 51 per cent showed complications in the form of uterine perforation (10 cases) or metastases (11 cases). One of the patients showed that besides uterine perforation there were also multiple (5) intestinal perforations with liberation of fecaliths into the peritoneal cavity. Fortunately, this particular patient, despite a prolonged stormy postoperative course, ultimately recovered. It is now 2 years since she was operated on and she is well.

Chorioadenoma destruens is not as malignant as choriocarcinoma. Its tempo of

Table IV. Criteria for the diagnosis of chorionic malignancy leading to hysterectomy in 41 cases

Criteria for diagnosis	No. of cases
Intraperitoneal hemorrhage coincident with mole (1,000 c.c. in 1 case); hysterectomy with the mole in situ	2
Lung metastasis in conjunction with mole; hysterectomy with the mole in situ; lungs treated by x-ray	2
Vaginal metastasis in conjunction with mole; hysterectomy with the mole in situ; vaginal growth removed surgically	1
Vaginal metastases appearing 12 days after curettage for mole; growth removed surgically	1
Age (42 years) and grandmultiparity (gravida ix, para viii); hysterectomy with the mole in situ	1
Uterine perforation as shown by: (a) uterine sound when a second curettage was to be performed for bleeding; (b) intraperitoneal hemorrhage occurring 30 to 85 days after curettage for mole in 5 cases; and 9 months after term delivery in 1 case	6
Biopsy of invasive mole after mole curettage	1
Clinical triad of chorionic malignancy from 26 days to 8 months after curettage for mole (In 2 cases laparotomy showed uterine perforation; biopsy of the growths found in the uterus showed chorioadenoma destruens)	26

growth is slower but it has the peculiarity of corroding and invading the surrounding tissues, and when it is located in the myometrium its tendency is to extend outward into the peritoneal cavity, causing uterine perforation with consequent hemorrhage. In 4 of the 10 cases of uterine perforation the blood found in the peritoneal cavity was from 1,000 to 2,000 c.c. (Table II). When the growth is located in the lower part of the uterus, it extends into the parametrium, vagina, and bladder. Removal of advanced growths in these regions along with hysterectomy involves bleeding which is difficult to control.

Metastasis in chorioadenoma destruens is indeed not as frequent nor as widely disseminated as in choriocarcinoma, which Acosta-Sison<sup>6</sup> found to occur in 96 per cent of 27 cases. However, the 27 per cent incidence of metastasis among the 41 cases of chorioadenoma destruens in the present study is high enough from the standpoint of the belligerence of the growth and the safety of the patient when not given early proper treatment.

Wei<sup>3</sup> of Taiwan gives the incidence of metastasis among 12 cases of chorioadenoma destruens to be 25 per cent. Prawirohardjo and associates<sup>4</sup> of Indonesia claimed that of 10 cases of chorioadenoma destruens 5 or 50 per cent showed metastases in such regions as the lungs, parametrium, and peritoneum. In one case, the metastasis was not only in the parametrium and the lungs but also in the brain.

Among our cases Table III shows that the sites of metastasis in 11 cases included the lungs, vagina, broad ligaments, parametrium, the labium majus, and mons veneris. In only one case were the metastases generalized (lungs, stomach, liver, kidneys, skin, and brain) in conjunction with hydatidiform mole diagnosed as invasive at autopsy.

From the evidence gathered from this study and the data given by Wei<sup>3</sup> and Prawirohardjo,<sup>4</sup> it is apparent that chorioadenoma destruens is not an innocent benign tumor. Perhaps Novak<sup>5</sup> gives the cor-

rect appraisal of its nature and behavior when he suggests that it be called a "milder variant of chorioepithelioma malignum." Prawirohardjo and associates call it "villous choriocarcinoma." The above terms clearly indicate the nonbenignity of the tumor.

### Clinical diagnosis

Table IV shows the criteria used in the diagnosis of chorionic malignancy which led to the performance of hysterectomy. Intra-peritoneal hemorrhage from uterine perforation by the mole was found in 2 cases. Lung metastasis in conjunction with hydatidiform mole was also found in 2 cases. In one case, vaginal metastasis was found in conjunction with mole. In these 5 cases hysterectomy was performed with the mole in situ. Intraperitoneal hemorrhage from a few days to as long as 9 months after the expulsion of the product of conception was found in 5 cases. In 26 cases, the clinical triad of (1) history of having expelled the product of conception, (2) uterine bleeding, and (3) enlargement and softening of the uterus at a time when it should be completely involuted was used in making the diagnosis of chorionic malignancy. All of these 26 patients showed growths in the uterus after hysterectomy.

According to Hertig and Mansell,<sup>2</sup> "chorioadenoma destruens may be suspected on clinical grounds, very rarely diagnosed by curettage but definitely confirmed by the excised uterus." The 26 cases diagnosed by the above triad support that statement.

### Mortality

Despite the severe complications of intra-peritoneal hemorrhage and metastases in 21 (51 per cent) of 41 cases, the number of deaths was only 4, giving a mortality of 10 per cent (Table V). This is in marked contrast to the series of 27 cases of choriocarcinoma reported by Acosta-Sison,<sup>6</sup> in which the mortality rate was 70 per cent.

The relatively low mortality rate of 10 per cent among these 41 cases of chorioadenoma destruens against the 70 per cent mortality of 27 cases of choriocarcinoma is



Table V. Mortality\*

<i>Cause of death</i>	<i>No. of cases</i>
Generalized metastases in conjunction with undiagnosed mole	1
Hemorrhage from uterine perforation	1
Hemorrhage during surgical removal of growth in left parametrium	1
Hemorrhage during surgical removal of growth in right parametrium, bladder, and vagina	1

\*Number of deaths, 4; mortality rate, 10 per cent.

due to: (1) the lesser malignancy and slower growth of chorioadenoma destruens, whose main characteristic is the corrosion and invasion of the surrounding tissues, in those cases of intraperitoneal hemorrhage from uterine perforation, (2) adequate blood replacement and timely performance of hysterectomy, and (3) early diagnosis and treatment before the growth had become widespread. Three patients could not be saved from hemorrhage on account of the

great extension of the growth, and in the one case of generalized metastasis in conjunction with hydatidiform mole, the patient was in extremis when seen and the diagnosis was made only at autopsy.

### Summary

Forty-one cases of chorioadenoma destruens are presented; 40 followed hydatidiform moles. The one exception followed a term delivery.

In 10 (24 per cent) of the 41 cases the uterus was perforated by the tumor.

Metastases occurred in 11 cases (27 per cent).

Four patients died, a mortality rate of 10 per cent.

Although chorioadenoma destruens does not grow as fast or metastasize as rapidly or as frequently to distant areas as choriocarcinoma, from the data of this study it cannot be regarded as a benign chorioma.

### REFERENCES

1. Ewing, J.: *Surg. Gynec. & Obst.* 10: 366, 1910.
2. Hertig, A. T., and Mansell, H.: *Hydatidiform Mole and Choriocarcinoma*, Armed Forces Institute of Pathology, Washington, D. C., 1956.
3. Wei, P., Pei-chuan, D., and Taluan, P.: *Trophoblastic Diseases at National Taiwan University Hospital*, Reports of the Institute of Pathology, National Taiwan University, No. 8, June, 1957.
4. Prawirohardjo, S., Martiono, K. S., and Tjokronegoro, S.: *Hydatidiform Mole and Choriocarcinoma in Indonesia*, Volume First Asiatic Congress of Obstetrics & Gynecology, Tokyo, Japan, 1957.
5. Novak, E.: *Gynecological and Obstetrical Pathology*, Philadelphia and London, 1947, W. B. Saunders Company.
6. Acosta-Sison, H.: *Acta med. philippina* 13: 241, 1957.

# Prerenal azotemia and hydatidiform mole

HAROLD SCHULMAN, M.D.\*

*Miami, Florida*

MOST standard references suggest that toxemia of pregnancy appearing before the twenty-fourth week of gestation should arouse the suspicion of hydatidiform mole. The commonly mentioned signs which might alert the clinician to this condition are: (1) uterine enlargement out of proportion to gestational age, (2) bloody discharge, (3) absence of fetal parts, (4) toxemia, and (5) elevated chorionic gonadotropin.<sup>11</sup>

In only one<sup>16</sup> of standard texts or recent reviews<sup>3, 4, 5, 7, 9, 14, 17</sup> is prerenal azotemia mentioned as a primary differential diagnostic enigma. So, because of the rarity of this problem and the complexities which the following case presented, it was felt to be worthy of report and study.

## Case report

A. G. O., a 47-year-old Negro woman, gravida xii, para ix, entered the Jackson Memorial Hospital emergency room on Feb. 25, 1959, with severe frontal headache and shortness of breath. The last normal menstrual period had been on Oct. 15, 1958, hence, a 16 weeks' gestation would be expected. There had been no prenatal care, a known 19 pound weight gain from 188 to 207 pounds, a slight amount of vaginal bleeding, dyspnea for 3 days, and three pillow orthopnea. Nausea and vomiting had occurred for 2 weeks.

Past history revealed a question of an elevated blood pressure during the last pregnancy, 6 years previously.

Physical examination showed a blood pressure of 190/100, pulse 120, and temperature 100° F., orally. The patient was obese and appeared quite dyspneic. The eyegrounds revealed arteriolar narrowing with no arteriovenous nicking, hemor-

rhages, exudates, or edema. The neck veins were distended in the sitting position, and fine moist râles were heard at both lung bases. The heart was enlarged, with the point of maximal impulse 2 cm. to the left of the midclavicular line. A Grade II aortic systolic murmur was present. Costovertebral angle tenderness was noted on the right. A soft nontender uterus extended to the umbilicus, and no fetal heart tones were heard. There was a slow oozing of blood from the cervical os, and lower extremity and pedal edema was present. Tables I and II present the laboratory findings.

She was started on Furofantin, digoxin, oral and intravenous hydrochlorothiazide, and an intravenous drip containing Unitensen and Apresoline. The blood pressure returned to normal while she was on the intravenous therapy, but would rise when it was discontinued. The pulmonary and circulatory status responded well to treatment.

The problems to be resolved were the question of a hydatid mole and whether intrinsic renal disease was present. An x-ray examination of the abdomen showed no fetal bones, and a fetal electrocardiograph revealed no fetal components. A sound was gently inserted into the uterine cavity, but when it reached a depth of 2 cm. bleeding was encountered and this procedure was immediately discontinued.<sup>2</sup> A quantitative Friedman test was positive only to a 1:10 dilution. An amniocentesis and dye injection study was attempted but, because of inability to obtain fluid, this could not be done.

An intravenous pyelogram produced no excretion of dye, but a retrograde study revealed pregnancy changes only. The blood urea nitrogen and potassium levels continued to rise, and the acidosis was refractory to therapy despite administration of alkali and a good urinary output.

The few white blood cells and bacteria in urine, elevated blood pressure, uremia, and acidosis were compatible with a diagnosis of chronic pyelonephritis, but the patient's edema, normal serum creatinine level, excellent urinary

*From the Department of Obstetrics-Gynecology, University of Miami School of Medicine-Jackson Memorial Hospital.*

*\*American Cancer Society Fellow, 1959.*

output, electrolyte excretion, and varying specific gravity were warning signs which, in retrospect, were not emphasized sufficiently. She became progressively more lethargic and chlorothiazide was discontinued on the sixth hospital day.<sup>13</sup>

Termination of the pregnancy was a constant consideration, but had not been elected because of the nebulous evidence of the effects of pregnancy on renal disease<sup>5, 8</sup> and consideration for the possibility of a viable fetus. A medical consultant suggested that this most likely represented chronic pyelonephritis or nephrosclerosis with a possible prerenal factor; but, since there had been no improvement, abortion should be performed. The day before the anticipated operation, the serum potassium reached a level of 6.8 mEq. and the electrocardiogram suggested hyperkalemic effects. That evening she died in her sleep having been observed 10 minutes prior to death sleeping comfortably with respirations of 20 per minute.

Postmortem examination revealed pulmonary congestion and cardiomegaly of 520 Gm. A hydatidiform mole was present which microscopically showed scant trophoblastic proliferation. There was an incidental finding of a 1 cm. adenoma of the right adrenal gland. The kidneys appeared grossly normal, the capsules stripping

off quite easily. Microscopic examination revealed ischemic glomeruli and cloudy swelling of the tubules. There was no evidence of pyelonephritis. Some of the arterioles were in varying degrees of spasm with thickening of the walls suggesting a recent hypertensive episode (Fig. 1). Final summation of this patient's death considering the clinical course and pathologic findings suggested death from hyperkalemia.

### Comment

The fatal outcome in this case is indeed tragic when one might have expected survival if there had been greater alacrity in evacuating the uterus. However, it does illustrate with startling accuracy the lethal potential of an undiagnosed hydatid mole. The clues which might reveal the diagnosis were faithfully pursued, leading to indecisive results.<sup>1, 10</sup> The red banner of warning was the presence of toxemia, but the "red herring" of confusion seemed to be the azotemia.

Azotemia has been classified by most renal physiologists into two components, renal and prerenal. The former refers to the presence of intrinsic renal disease, that is, a distinct

### Table I. Urine

<i>Date</i>	<i>Na</i> ( <i>mEq./</i> <i>L.</i> )	<i>K</i> ( <i>mEq./</i> <i>L.</i> )	<i>Cl</i> ( <i>mEq./</i> <i>L.</i> )	<i>Specific</i> <i>gravity</i>	<i>Fluid</i> <i>intake</i>	<i>Output</i> <i>volume</i>	<i>Albumin</i> ( <i>random</i> <i>specimen</i> )	<i>pH</i>	<i>Microscopic</i> ( <i>6 WBC with</i> <i>clumps</i> )
February 26			32.7	1.010	1,940	2,050	30	4.5	
February 27			36	1.014	2,490	2,825	8		8-10 WBC glitter cells 1-2
February 28			31	1.003	2,950	2,625	10	4.5	
March 1	75.5	47	25.1		3,335	2,600			
March 2	47.5	28	22.4		2,890	2,315			
March 3	55.6	47		1.008	1,730	2,375	20		

Table II. Blood

[illegible]

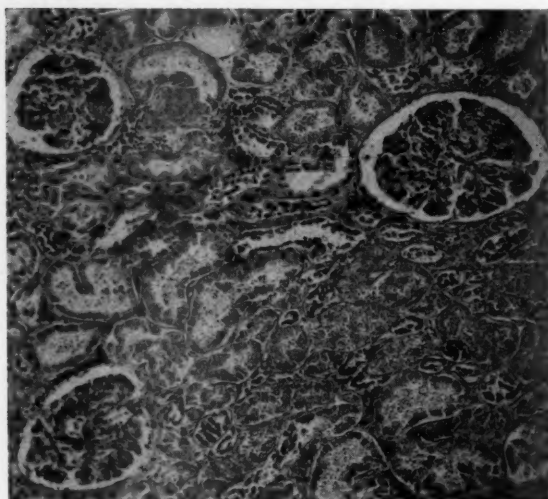


Fig. 1. Section of kidney revealing ischemic glomeruli and some cloudy swelling of the tubules. No evidence of pyelonephritis, tubular necrosis, or nephrosclerosis.

morphologic glomerulotubular or interstitial lesion. In contrast, prerenal azotemia generally refers to nitrogen retention in the absence of pathologic kidney changes. It is usually due to a decrease in renal blood flow and has been most frequently described in such conditions as vomiting, diarrhea, hepatorenal syndrome, diabetes, traumatic shock, circulatory collapse, burns, and myocardial infarction.<sup>7</sup> One might say, then, that it occurs when there is a change in the circulatory dynamics of the kidney.

The kidney has been a primary focus of attention for the student of eclampsia—pre-eclampsia for obvious reasons. Nitrogen retention is not a usual manifestation except when oliguria or anuria is present. Considerable controversy has raged whether toxemia does produce specific parenchymal changes in the kidney. Most commonly described is thickening, reticulation, and even splitting of the basement membrane of the glomerulus, or “swollen ischemic glomeruli.”<sup>12</sup> However, the erratic occurrence of these findings at autopsy and in renal biopsy specimens suggests that these are not pathognomonic changes, but are secondary to circulatory or electrolyte effects.<sup>6, 15</sup> It cannot be emphasized too strongly that, when renal failure occurs during toxemia in the absence of

hemorrhagic shock, it is not the result of widespread alteration in renal parenchyma but is extrarenal in origin, and this factor must be diligently searched for.<sup>15</sup> Therapy must then be directed toward alleviation of this factor; therefore, it might be against vasospasm, electrolyte imbalance, dehydration, or, as in this case, only by evacuation of the uterus, thereby freeing the circulatory system from the effects of the substance or lack of substance which produces pre-eclampsia.

When the differential diagnosis of azotemia is approached in a patient with toxemia and renal failure, the first question which must be answered is why is renal failure present. A history of hemorrhage or the presence of abruptio placentae would answer this relatively easily. These factors having been ruled out, an accurate fluid intake and output should begin. If azotemia is present, the following studies should reveal to the clinician the rare but very important presence of prerenal azotemia: (1) specific gravity being dilute (less than 1.010) or concentrated (more than 1.010) suggests good renal reserve; (2) a serum creatinine of normal value in the face of elevated BUN suggests normal tubular function; (3) 24 hour urine electrolyte studies showing excretion of near normal values suggests functioning tubules; (4) renal biopsy, if available, would be a valuable diagnostic tool.

Efforts should be made to correct vasospasm which may be the primary factor in the pathogenesis of this problem.

### Summary

A fatal case of hydatidiform mole associated with prerenal azotemia is reported because of the confusion and diagnostic problems which it presented. A brief review of current concepts of the role of the kidney in toxemia is given with comments on the pathogenesis of prerenal azotemia. The rarity of this combination of hydatid mole and elevated blood urea nitrogen is emphasized, but the widespread usage of antihypertensive drugs and diuretics may lead to more frequent occurrence.



#### REFERENCES

1. Acosta-Sison, H.: *AM. J. OBST. & GYNEC.* 55: 132, 1947.
2. Acosta-Sison, H.: *Obst. & Gynec.* 12: 205, 1958.
3. Clayton, S., and Oram, S.: *Medical Disorders of Pregnancy*, London, 1951, J & A Churchill, Ltd.
4. Coppleson, M.: *J. Obst. & Gynaec. Brit. Emp.* 65: 238, 1958.
5. Dieckmann, W. J.: *Toxemia of Pregnancy*, ed. 2, St. Louis, 1950, The C. V. Mosby Company, p. 475.
6. Dieckmann, W. J., et al.: *AM. J. OBST. & GYNEC.* 73: 1, 1957.
7. Fishberg, A.: *Hypertension and Nephritis*, ed. 5, Philadelphia, 1954, Lea & Febiger, pp. 50, 57.
8. Friedberg, V.: *Zentralbl. Gynäk.* 80: 1289, 1958.
9. Hertig, A. T., and Sheldon, W. H.: *AM. J. OBST. & GYNEC.* 55: 1, 1947.
10. Kenney, R. A.: *J. Obst. & Gynaec. Brit. Emp.* 57: 17, 1950.
11. King, G.: *Proc. Roy. Soc. Med.* 49: 381, 1956.
12. McKay, Donald, et al.: *AM. J. OBST. & GYNEC.* 66: 507, 1953.
13. Mule, J. G., et al.: *AM. J. OBST. & GYNEC.* 74: 526, 1957.
14. Novak, J., and Rubin, I. C.: *Integrated Gynecology II*, New York, 1956, McGraw-Hill Book Company, p. 189.
15. Ober, Wm., et al.: *Am. J. Med.* 21: 781, 1956.
16. Smith, H. W.: *The Kidney*, New York, 1951, Oxford University Press, pp. 635, 753.
17. Theobald, G.: *Pregnancy Toxemias*, New York, 1956, Paul B. Hoeber, Inc., p. 38.

## CURRENT OPINION

### Pertinent comments

## A note on race-specific congenital malformation rates

TODD M. FRAZIER, Sc.M.

*Baltimore, Maryland*

A REVIEW of congenital malformation rates derived from information on birth certificates submitted to the Baltimore City Health Department agrees with previous reports<sup>1, 2</sup> in the finding that polydactylism occurs far more often among Negro babies than among white babies. The purpose of this note is to present race-specific rates for all reported anomalies and for congenital malformations, excluding polydactylism.

During the 5 year period, 1954-1958, there were 120,127 live births among the resident population of Baltimore, a city of nearly a million inhabitants. A physician or midwife attending a delivery is required to submit to the Baltimore City Health Department a birth certificate which, in addition to identifying information, includes a question concerning the presence of and type of congenital malformations noted at birth. To the extent that malformations are recognized and reported, the birth certificate provides a source of information concerning the incidence of anomalies among deliveries in an unselected population. Because of underre-

porting of malformations on birth certificates, the rates reported herein should be interpreted as an underestimate of the true frequency in a general population.

Table I shows congenital malformation rates for live births among Baltimore residents during the period 1954-1958. The nonresident births, which include difficult obstetrical cases referred to the city's medical centers, have been excluded. Among the 71,032 white babies born there were 477 with malformations reported, a rate of 6.8 per 1,000 live births. The corresponding rate for the 49,095 non-white babies was 7.9 per 1,000 live births. Thus, for all reported congenital malformations the rate for the Negro race is about 16 per cent greater than the rate for the White race.

If malformations of "bone and joint" (International Statistical Classification No. 758) are excluded, the race-specific rates are 4.8 for white babies and 3.0 for Negroes. Bone and joint malformation rates are 2.0 and 4.9 per 1,000 for the white and non-white, respectively, indicating more than a twofold increase in malformations of this general type among Negro infants.

A search of the 388 birth certificates for which bone and joint malformations were

*From the Department of Obstetrics,  
Johns Hopkins University and Hospital,  
and the Bureau of Biostatistics,  
Baltimore City Health Department.*

**Table I.** Selected congenital malformation rates by race

<i>Type of malformation</i>	<i>Number</i>			<i>Rate per 1,000 live births</i>		
	<i>Total</i>	<i>White</i>	<i>Non-white</i>	<i>Total</i>	<i>White</i>	<i>Non-white</i>
All malformations except bone and joint	478	333	145	4.0	4.8	3.0
Malformation of bone and joint	388	144	244	3.3	2.0	4.9
Polydactylism	200	21	179	1.7	0.3	3.6
All other bone and joint malformations	188	123	65	1.6	1.7	1.3
Total	866	477	389	7.3	6.8	7.9
Malformation rate excluding polydactylism					6.5	4.3

reported revealed that, of the 244 anomalies of this type among non-whites, 179, or about 74 per cent, were births in which polydactylism was reported. The incidence of this malformation among Negroes was 3.6 per 1,000 live births, a twelvefold increase over the rate of 0.3 per 1,000 noted for white infants. The incidence of all other bone and joint malformations was approximately the same in the two races.

The last line of Table I shows the race-specific malformation rates obtained when polydactylism is excluded. Here the rate for white live births, 6.5 per 1,000, is about 50 per cent greater than the rate of 4.3 obtained for non-white births. When all reported malformations are included, the Negro malformation rate is higher than the rate for white infants—7.9 compared to 6.8

per 1,000 births. When polydactylism is excluded, the congenital malformation rate is higher for the white race—6.5 compared to 4.3 per 1,000 for Negroes.

The possibility of observer differences must be considered. Thus, if there was a tendency for the Negro patients to be attended by less astute observers, then polydactylism might be noted whereas other more subtle anomalies might be missed. The only direct evidence against such observer bias rests in the statistics from the Johns Hopkins Hospital where, with the same or comparable observers for the two racial groups, the statistical difference noted for the entire sample also pertains. Thus, the greater incidence of congenital malformations can be awarded to either the Negro or the white race depending on the inclusion or exclusion of polydactylism.

#### REFERENCES

1. Wallace, H. M., Baumgartner, L., and Rich, H.: *Pediatrics* 12: 525, 1953.
2. Barsky, A. J.: *Congenital Anomalies of the*

*Hand and Their Surgical Treatment*, American Lecture Series, No. 311, Springfield, Ill., 1958, Charles C Thomas, Publisher.

## A rapid method for the office diagnosis of candidiasis

JED E. GOLDBERG, M.D.

*Tulsa, Oklahoma*

CANDIDA vaginitis has appeared with increased frequency with the advent of the "broad-spectrum" antibiotics. The diagnosis is usually not too difficult to make clinically but, occasionally, the characteristic lesions are not seen. The physician must then rely on smears and/or cultures or else prescribe "shotgun" medications with limited efficacy. Cultures are expensive and during the incubation period the disease continues untreated. Most severe cases can be diagnosed from the wet smear with use of saline but this involves in most cases a tedious and oftentimes fruitless search through the vaginal debris in order to spot the characteristic pseudomycelia. The use of potassium hydroxide instead of saline will dissolve much of this debris but a sharp search for pseudomycelia will still take up valuable time. Cohen,<sup>1</sup> a dermatologist, suggested the addition of Parker ink to potassium hydroxide to facilitate the rapid diagnosis of fungus infections of skin and nails by staining the mycelia. It was felt that the gynecologist

might benefit from this technique in the easier diagnosis of vaginal candidiasis.

The solution is made by adding 10 c.c. of Parker 51 Superchrome blue-black ink to 20 c.c. of 20 per cent potassium hydroxide. In all patients with vaginitis a wet smear is first made with use of saline solution. If trichomonads are not seen or if candidiasis is suspected clinically, 1 or 2 drops of the special stain are added to the original smear which is allowed to stand for 5 minutes and then is examined under low and high power. The outlines of pseudomycelia are quite easily seen against a pale blue background. There is a minimum of confusing cellular debris.

No originality is claimed by me for this technique, but it was felt that the gynecologist should be exposed to this rapid and accurate method for office diagnosis of a most common condition.

---

### REFERENCE

1. Cohen, Morris M.: Bull. School Med. Univ. Maryland 43: 20, 1958.



## Threatened abortion

SAMUEL D. SOULE, M.D.

*St. Louis, Missouri*

WITHOUT attempting an exhaustive review of the literature, one may refer to the current periodicals of the past year to obtain a vista of the confusion which encompasses the problem of bleeding during the first trimester of pregnancy. A review of end results of any series of abortions confronts the reader with a maze of variables which cloud lucid analysis. In any such group there are a considerable number of patients with blighted ova, faulty implantation, or other organic defects which are incompatible with successful maintenance of pregnancy. Patients who threaten to abort a given individual pregnancy are frequently not separated in analysis from patients with cases of habitual abortion. Diametrically opposing conclusions as to the value of such diagnostic procedures as pregnanediol determinations, vaginal cytology, or gonadotropic hormone studies may be noted. One author unequivocally states that no therapy is of any value whereas others report excellent results with various lines of treatment.

Also, one must distinguish between pathologic bleeding and physiologic bleeding. Eastman observes that 2 out of 10 pregnant women have vaginal spotting or actual bleeding during the early months of gestation. Yet, of these 2 who bleed, only one actually aborts. Physiologic bleeding is that which is analogous to the placental sign described by Hartman in the monkey. The blood seems to make its way from ruptured paraplacen-

tally situated blood vessels and eroded uterine epithelium into the uterine cavity.

In 1944 Hertig and Livingstone offered a concept of "pregnancy salvage." Threatened abortion occurs in at least 16 per cent of all pregnancies. Approximately 10 per cent of human pregnancies end in abortion. On the basis of a series of 1,000 cases examined embryologically and pathologically, approximately one third of spontaneous abortions were theoretically capable of being salvaged at the time the patient was first seen by the physician. After studying the threatened abortions which do not abort regardless of treatment employed and those which abort if untreated, Hertig concluded that approximately 60 per cent of threatened abortions under adequate treatment may fail to abort.

Hodgkinson and co-workers made an effort to gain some insight into the potential salvage for the patient with threatened abortion when the major symptom was bleeding. A control group of patients was treated with bed rest and sedation and the pregnancy salvage was 15.5 per cent. Examination of abortuses expelled intact with the amniotic sac revealed normal specimens in 31.3 per cent. The *potential* salvage was adduced by adding the percentage of patients in the control group who were still pregnant without treatment (15.5 per cent) to the percentage of normal abortuses (31.3 per cent), or a total of 46.8 per cent.

Edith Potter observed that, among 1,500 aborting women, in only 20 per cent were normal embryos present and over half of these had been dead for a considerable time before abortion. Most abortions occur because the embryo is abnormal and with such

*From Washington University School of Medicine, Department of Obstetrics and Gynecology, and the Department of Obstetrics and Gynecology, Jewish Hospital.*

an embryo abortion is inevitable. Possibly in 10 per cent of abortions the underlying etiology lies with an intrinsic maternal condition that is responsible for the expulsion. After bleeding begins, ordinarily it is already too late for any variety of treatment to do much good. Half of the time the symptoms of the threatened abortion will disappear and the pregnancy will continue normally. Potter thus concluded that "probably less than 10 per cent of the total could have been saved by any form of treatment." Some of us who are committed by our personal philosophy to employ some form of treatment would prefer to paraphrase this conclusion of Potter to read: Possibly some 10 per cent of the total series *might* have been saved by *some* form of treatment.

When a given patient calls her obstetrician and reports the presence of bleeding, with or without cramps, pain, pelvic pressure, or other symptoms of threatened abortion, there is no available time to consider the possibility or probability of this particular episode's being one of inevitable or salvageable threatened abortion. It is at this time that each of us is committed to a concept of procedure which represents his own experience. This discussion finds no fault with such therapy as watchful observation, bed rest and sedation, opiates, thyroid, vitamins E, K, C, or P, physiotherapy (especially in habitual abortion), hormone therapy, or any other procedure which in the armamentarium of any one of us has his own approval.

When the patient is threatening to abort, it may be difficult or impossible to determine clinically whether or not the pregnancy can be salvaged. Hence, all threatened abortions must, in the absence of more precise clinical signs, be considered salvageable until proved otherwise. It is evident that any rational treatment of threatened or habitual abortion must be directed toward saving the pregnancies that are fundamentally salvageable when the patient is first seen, even though the physician does not at that time know whether or not such a pregnancy can be saved. The percentage of successfully treated threatened and habitual abortions must

therefore consist of the group of pregnancies that would not have been aborted anyway, in addition to those that are salvageable when the patient is first seen.

Let it be granted that a certain percentage of patients who threaten to abort will carry on successfully with no therapy. Consideration of salvageable pregnancies commits those of us who believe in the efficacy of hormone therapy to initiate such treatment promptly upon exhibition of symptoms of threatened interruption of pregnancy. Progesterone has been the honored parent of a series of steroid compounds employed in the maintenance of pregnancy, where it serves as a blocking agent in the myometrial cell with action comparable to procaine block.

One may question whether *any* therapy is indicated. Here again one must exert a differential attitude between threatened abortions which are habitual and those which are nonhabitual in nature.

Colvin and co-workers, in reporting a series of 1,570 threatened abortions treated by bed rest and sedation, noted that only 62 (3.9 per cent) could theoretically have been prevented by hormone or vitamin treatment. Eastman, in discussing this presentation, comments that one must face the fact that 19 or 20 cases must be treated needlessly in order that the occasional patient in whom various therapeutic measures may be effectual is helped. Lock stated that little or nothing is gained by the administration of hormones, minerals, vitamins, or other drugs to the patient with threatened abortion. Equally good results are obtained by simple supportive measures as with intensive medical treatment. Hollstein found it possible to maintain 50 per cent of 172 cases of threatened abortion and concluded that one should always try to prevent an abortion which is threatened. Hodgkinson and associates reported that in a luteoid-treated group 39.4 per cent of the pregnancies continued, as compared with 15.5 per cent in their control group noted above. Also, in the control group 81.2 per cent of the patients aborted within 2 weeks of onset of symptoms, whereas in the luteoid-treated patients the dynamics of abortion

were delayed 4 weeks or longer in 46 per cent of those who aborted. Goldzieher stated that the true efficacy of a treatment is difficult to estimate. If a given form of treatment is evaluated in patients with low pregnanediol excretion (where 80 to 100 per cent may be expected to abort without treatment) the likelihood of a statistically meaningful effect is proportionately greater. The prognostic significance of low pregnanediol excretion is very grave. There is definite evidence, as well as some inconclusive reports, of benefit from progesterone therapy, particularly in patients with low pregnanediol excretion.

When a given patient notifies her obstetrician that she is bleeding, however, there is not time available for him to collect a urine specimen for determinations of progestational

excretion products prior to recommending therapy. There is a distinct temporal correlation between onset of symptoms and onset of therapy in so far as prognosis is concerned. Therefore, if one be of the hormone school of therapy, treatment is begun as promptly as possible following onset of symptoms. It may not be amiss in a day of increasing availability of oral steroids to give all patients, in their first trimester, an envelope containing an appropriate amount of such hormones as the physician believes in. Then, should treatment become necessary, it can be initiated within minutes after onset of bleeding. Subsequently one could carry out such diagnostic procedures as may be necessary to rule out other causes of bleeding, to estimate the need for hormone therapy, and possibly to predict the clinical outcome.

## Reviews | Abstracts

*Edited by*

LOUIS M. HELLMAN, M.D.

### Reviews of new books

**The Surgeon and the Child.** By Willis J. Potts. 225 pages, 22 illustrations. Philadelphia, 1959, W. B. Saunders Company. \$7.50.

This book is by way of being a tour de force of textbook writing such as few surgeons could have attempted. Dr. Potts brings it off beautifully. His enormous clinical experience and his substantial contributions to pediatric surgery are delightfully counterpoised by a light, airy, charmingly readable text. The book makes no claim to be comprehensive, yet some 29 brief chapters allow Dr. Potts to express himself in his lucid and pithy style on most of the important surgical lesions of infancy and childhood. Dr. Pott's approach is disarmingly candid, and just when one would be on the point of taking issue with him on some controversial question, one finds him stating quite frankly that there may be those who would disagree with him and that quite possibly they may be right but this is his own approach and practice.

The book can be read in an evening. For the medical student or pediatric or surgical house officer it constitutes a splendid introduction to pediatric surgery. For the pediatrician and the pediatric surgeon, it contains the unequivocal opinions and the evaluated experience of one of the leaders in the field.

**Reversible Renal Insufficiency.** By Donald H. Atlas and Peter Gaberman. 233 pages, 19 figures, 4 tables. Baltimore, 1958, Williams & Wilkins Company. \$7.00.

The authors of this book state in their preface that they had to make a choice as to whether they should write a comprehensive encyclopedic book for the expert in the field or a simpler, more concise one of general interest. They

wrote one which tends to be more a concise monograph. The title indicates the authors' dislike for the term "acute renal failure." The reason that the use of the word "failure" implies bankruptcy of function, whereas "insufficiency" denotes a more hopeful prognosis is eminently justifiable.

The book is divided into two parts. Part I deals with "Reversible Acute Renal Insufficiency" in eight chapters. Part II deals with "Reversible Chronic Insufficiency" in only two chapters. The coverage in Part I is reasonably extensive. Part II deals only with those "conditions associated with chronic renal insufficiency which are amenable to arrest, amelioration, or cure."

In general this book is well written and authoritative. On reading it one gets the impression it is written by clinicians for clinicians. The causes of acute reversible renal insufficiency occurring in pregnancy are listed and some of them are discussed in the text. The coverage here is not extensive, but one could not expect this in a concise description of such an intensive subject as acute renal insufficiency. It is this reviewer's opinion that the authors of this book have in general achieved their objective. It is a welcome addition to the growing list of monographs in this field.

**Introduction to Colposcopy.** By Karl A. Bolton (cooperating in Pathology, William E. Jaques). 76 pages, 53 figures. New York, 1960, Grune & Stratton, Inc. \$7.75.

Colposcopy was introduced by Hinselman in 1925 and has been quite generally accepted in Europe. However, it is employed rarely in this country. The reason may well be the lack of



understanding of its use as well as its value. The present book is an effort to bring colposcopy to the attention of the gynecologists of this country in an easily understandable manner. It is not overburdened with technical terms but rather explains in simple language its value and method of operation.

The various entities one might encounter in examining the cervix are described grossly, microscopically, and as they appear through the colposcope. These descriptions are not cumbersome in detail but accurate and sufficient for the average observer. The colored illustrations portray the appearance of these lesions quite well.

This small book will serve well those who develop an interest in this addition to diagnostic procedures. It may help to stimulate an increased interest in colposcopy in this country.

**Pratique obstétricale.** By M. Lacomme. 2 volumes, 2,595 pages, 528 figures, 15 tables, 4 color plates. Paris, 1960, Masson et Cie. 23,000 fr.

*Pratique obstétricale* is a most aptly named work, for the intention of the author has been to emphasize the practical aspects of his subject. While there are no distinct chapters on anatomy, embryology, and physiology, these basic sciences are generally integrated into the text and this is particularly true for the physiology of normal labor.

Professor Lacomme has chosen to write in a style that is meant to resemble the familiar, spoken word of a bedside teacher, and the point of view is his own; only secondarily are varying opinions introduced. Frequently the text almost takes the form of a Socratic dialogue. Presented in two large volumes, running to 2,595 pages, this work allows the author ample space to fully and simply treat all the major facets of obstetrics. Current advances in areas such as isoimmunization, hypofibrinogenemia, the incompetent cervical os, postmaturity, and electrohysterography are adequately treated. Professor Lacomme stresses the need for a broad understanding of normal labor; to this end, numerous concrete, charted examples of both normal and abnormal labor are presented, along with the specific management and reasoning in each case.

Two interesting chapters deserve mention: one is an objective presentation and analysis of G. D. Read's "natural childbirth," and of the Franco-Russian "psychoprophylactic" methods

of delivery. Specific techniques and outlines of lectures, as well as the theoretical bases of the two approaches, are discussed. The other chapter is a sociomedical survey of the present-day evolution of obstetrics, with statistics comparing conditions in France to those in other countries, as well as similar data regarding districts in France. There are over 500 illustrations. While the drawings are excellent, the photographs are too small, and of below standard quality. Only a few chapters contain a bibliography (where the author, as he states, felt the need to draw from other sources, rather than from his own experience). The chapter on forceps revealed a surprising deficiency in that there is no mention of either a sliding-lock type of forceps, or of any forceps designed specifically for the aftercoming head.

This is very clearly the work of a seasoned and thoughtful teacher; it is peppered with numerous fine points and personal reflections and is presented with dignified modesty. The book can be read with considerable profit by any physician practicing obstetrics who is able to read the French text.

**Roentgens, Rads and Riddles—a Symposium on Supervoltage Radiation Therapy.** Edited by Milton Friedman, Marshall Brucer, and Elizabeth B. Anderson. 495 pages, illustrated. Washington, D. C., 1959, United States Government Printing Office. \$3.50.

*Roentgens, Rads and Riddles* is a most interesting collection of papers relating to supervoltage radiation therapy and, for this reason, it is somewhat difficult to wade through except for short sittings.

The title of this book suggests some humorous content but any humor present is limited to a quirk on the part of the person who titled the book. This collection of papers presented at the Oak Ridge Institute of Nuclear Studies in July, 1956, represents the thoughts and opinions of a large number of recognized authorities in the field of radiation. Despite the lapse of several years, the material is still of great interest, both from a historical as well as a current therapeutic point of view. It should be widely read by all serious students and practitioners of supervoltage radiation therapy. Those who may have limited interest, such as gynecologists interested in the treatment of pelvic cancer with supervoltage equipment, might profit by reading those sections pertaining to their specific

fields of interest. The editors of this symposium are to be congratulated for presenting so much of the candid discussions following each presentation, for it is in this material that a wealth of opinion, controversial and otherwise, reflecting the vast experience of the many participants, can be obtained.

**Strahlenbehandlung in der Gynäkologie.** By Julius Ries and Josef Breitner. 219 pages, 60 figures. München, 1959, Urban & Schwarzenberg. DM 32.

The somewhat ambitious title of this monograph does not adequately represent its contents which consist of a rather detailed description of the radiotherapy applied in the first gynecological division of the University Hospital in Munich. The rich body of material consists of over 25,000 cases of cancer and almost 14,000 cases of different benign disorders treated by radiation in the years from 1912 to 1959.

The book is divided into two sections; the first, a general part (75 pages) deals mainly with basic radiation physics, dosimetry, and the biological effects of radiation. The second, the "special section," describes methods of treatment and discusses complications and results.

The first section seems to be superfluous for a radiologist. For other practitioners, it is certainly too detailed. It is lacking in the description of any form of supervoltage therapy which is rapidly displacing conventional x-ray treatment, and this lack makes the book outdated. It contains a fairly rational methodology of intracavitary radium application which still remains the treatment of choice.

The second section is subdivided into chapters dealing with different sites of the disease. In addition to the cancers of the cervix, corpus, vagina, vulva, and ovaries, it also contains a chapter on the radiation therapy of cancer of the breast. This chapter is treated rather summarily, and it is doubtful whether it belongs in this book. The value of preoperative irradiation is, however, justly stressed. A chapter dealing with radiotherapy of benign conditions, especially uterine bleeding, seems to have only historical value since, with the exception of radiocastration, all other indications for radiotherapy listed there have been abandoned. The use of intracavitary

radiation for uterine bleeding is no longer practiced in this country and radiocastration is performed by external irradiation only.

The last third of the book deals with complications of radiotherapy. It contains the detailed description of patient care, dietary instructions, methods of charting, and follow-up of the patient. A short chapter about hormone therapy and cancerocidal drugs is also included. There are a number of statements in the book which are either very much outdated or are unproved. There is hardly any institution which would treat a cancer of the cervix during pregnancy with radium and permit the conclusion of pregnancy to full term. It is also questionable whether 80 r to the spleen will arrest bleeding from a radiation injury to the rectum or bladder. Treatment of the pituitary in gynecological hormonal disorders is not practiced any more.

The book is as stated a thorough description of the treatment in Munich and there is almost no consideration given in the discussion to any contribution of the British, French, and American therapists. The literature index shows almost exclusively German sources. The treatment results, however, are excellent; for instance, 48 per cent symptom-free 5 year survivals from cancer of the cervix in the years 1940-1952 (2,634 of 5,420 patients). It is certainly valuable for specialists to be able to partake in the experience of such a large patient material. The use of a nonrigid radium method with control of the dose in the bladder and in the rectum by means of the "momentandosimeter" by Bomke and Eberle is an asset worth imitation. Such individualized treatments must be necessarily restricted to larger centers with more sophisticated equipment and experience. The fractionation of the radium dose in three insertions has long since been reduced to two in most therapy centers and it seems not justified clinically, especially in view of the increased exposure to personnel by frequent handling of high intensity radium applicators.

For a student in the radiotherapy of gynecological cancer it is a valuable book. It serves again to show that the ultimate success does not depend on the use of a particular method or on the newest type of equipment, but on the skill and experience of the therapist.

## Books received for review

- Anatomy—A Regional Study of Human Structure.** By E. Gardner, D. J. Gray, and R. O'Rahilly. 999 pages, 40 tables, 82 figures, 65 plates. Philadelphia, 1960, W. B. Saunders Company. \$15.00.
- Atlas der gynäkologischen Operationen.** By O. Käser and A. Iklé. 451 pages, 720 figures. Stuttgart, 1960, Georg Thieme Verlag. \$35.25.
- Atlas of Electromyography.** By N. Roselle and contributors. 159 pages, 183 figures. Louvain, 1959, E. Nauwelaerts.
- Childbirth: The Modern Guide for Expectant Mothers.** By C. R. A. Gilbert. First edition. 256 pages, 7 figures. New York, 1960, Hawthorn Books, Inc. \$3.95.
- Christopher's Textbook of Surgery.** By Loyal Davis. Seventh edition. 1,551 pages, 1,597 illustrations. Philadelphia, 1960, W. B. Saunders Company. \$17.00.
- Congenital Malformations of the Uterus—Results of the Strassmann Metro-Plastic Operation.** By G. A. J. Dunselman. 192 pages, 57 pages, 57 figures, 15 tables. Helmond, 1959, N. V. Boekdrukkerij.
- Current Therapy—1960.** By Howard F. Conn. 808 pages. Philadelphia, 1960, W. B. Saunders Company. \$12.00.
- Electrohysterography.** By Saul David Larks. 123 pages, 44 figures, 2 tables. Springfield, Ill., 1960, Charles C Thomas, Publisher. \$5.75.
- The Low-Sodium, Fat-Controlled Cookbook (Completely Revised).** By A. S. Payne and D. Callahan. 465 pages. Boston, 1960, Little, Brown & Company. \$4.75.
- Oxygen Supply to the Human Fetus—A Symposium.** Edited by James Walker and Alec C. Turnbull. 313 pages, 136 figures, 47 tables. Springfield, Ill., 1959, Charles C Thomas, Publisher. \$10.50.
- Die Sexualhormontherapie in der Gynäkologie.** By Friedrich Hoffmann. Third edition. 182 pages, 55 figures. Leipzig, 1959, Johann Ambrosius Barth. DM 11.
- Stress and Cellular Function.** By H. Laborit (in collaboration). 255 pages, 61 figures. Philadelphia, 1959, J. B. Lippincott Co. \$7.50.
- A Textbook of Gynecology.** By Laman A. Gray. 470 pages, 324 figures, 6 plates. Springfield, Ill., 1960, Charles C Thomas, Publisher. \$15.50.
- Textbook of Human Embryology.** By R. G. Harrison. 244 pages, 144 figures, 1 table. Springfield, Ill., 1959, Charles C Thomas, Publisher. \$10.50.

## Selected abstracts

### **Acta obstetricia et gynecologica scandinavica**

*Vol. 38, Suppl. 4, 1959.*

\*Soiva, K., Gronroos, M., and Rinne, U. K.:  
Effect of Psychic and Painful Stimuli  
on the Reproductive Organs of the Female Rat, pp. 1-22.

Soiva, Gronroos, and Rinne: Effect of Psychic  
and Painful Stimuli on Reproductive  
Organs of Female Rat, pp. 1-22.

Female rats, in groups of 11 or 12 animals, were

subjected to stress treatment, which was mainly of psychic character and which lasted for 2, 14, and 28 days, respectively. Each test group had a control series of similar weight. Evaluation included vaginal smears, hormonal analyses, determination of weight of adrenals, hypophyses, and ovaries, the number of primary, Graafian, and atretic follicles and of corpora lutea in the ovaries; for some of the animals the gonadotrophin content of the hypophysis suspension was also determined, while in others the relative number of PAS-positive cells was counted.

The experimental method produced an in-

\*These articles have been abstracted.



crease in the size of the adrenals even after a treatment of 2 days but the adaptability of the animals could tolerate a treatment lasting even 28 days. After the 2 day treatment, ovarian hyperemia and enlargement, as well as partial degranulation of the PAS-positive cells of the anterior lobe of the hypophysis, were noted. In the 14 day test group there were observable disturbances in the hormonal functions of the reproductive organs. In the 28 day test group a definite suppression of the hormonal function was observed which was accompanied by similar changes in the hypophysis and the ovaries. This study supports the idea that the increased gonadal function in acute stress, as well as the decreased function with gonadal atrophy in prolonged stress, is attributable to a changed production of gonadotrophins by the anterior lobe of the hypophysis and not due to changed sensitivity of the reproductive organs to gonadotrophin.

*Robert E. L. Nesbitt, Jr.*

*Fasc. 4, 1959.*

\*Furuhjelm, M.: Transplantation of Foetal Membranes in Cases of Secondary Amenorrhea, Caused by a Non-Reacting Endometrium, p. 453.

\*Zondek, B., and Pfeifer, V.: Further Studies on Urinary Oestriol Excretion During Pregnancy and Its Significance for Estimation of Placental Function and Dysfunction in Advanced Pregnancy, p. 742.

**Furuhjelm: Transplantation of Foetal Membranes in Cases of Secondary Amenorrhea, Caused by a Non-Reacting Endometrium, p. 453.**

Fetal tissues induce special differentiation of embryonic tissue. Transplantation of fetal membranes has been used with favorable results in cases of vaginal aplasia and cervical or uterine atresia. This action of fetal membranes suggested to the author the use of this technique in patients with amenorrhea with normal hormone excretion but an atrophic endometrium—the hypothesis being that this fetal tissue would induce growth of new endometrium from undifferentiated mesenchymal tissue in the uterine wall.

In order to increase uterine vascularization, estradiol (5 mg.) and progesterone (25 mg.) were given preoperatively for 2 days. After a curettage on the third day, small pieces of fresh fetal membranes were applied to the walls of the

uterine cavity in 4 cases. The uterus was firmly packed and the tamponade was left in place 4 or 5 days. Each patient had not responded to previous lengthy treatment with hormones.

In each of the 4 cases of transplantation, menstruation occurred within 8 weeks, but in one case the treatment had to be repeated 3 times before regular menses continued. The time of observation varied between 14 months and 2 years. The favorable results could be reasonably attributed to the transplantation.

*Robert E. L. Nesbitt, Jr.*

**Zondek and Pfeifer: Further Studies on Urinary Oestriol Excretion During Pregnancy and Its Significance for Estimation of Placental Function and Dysfunction in Advanced Pregnancy, p. 742.**

The authors devised a technique whereby estriol is separated from estrone-estradiol by partition between benzene-petroleum, ether, and water. The determination of estriol was performed photo-fluorometrically with an experimental error of  $\pm 15$  per cent, and the quantitative estimation of this hormone in the urine in advanced pregnancy was recommended for evaluation of the normal and disturbed function of the placenta. Because of fluctuations throughout the day, 24 hour urine specimens were recommended for analysis. The placenta seemed to possess the capacity of functional regeneration; furthermore, the daily variations in estriol excretion during pregnancy were considerable—up to 60 per cent. The excretion of estriol did not change before or on the day of delivery, or during delivery. In the case of twins, the estriol excretion was increased in some cases, but this was not a uniform finding.

The authors found that fluctuations of estriol excretion in toxemia of pregnancy occurred more frequently than in normal pregnancy. They concluded that low absolute estriol values are of more serious prognostic significance in toxemic than in normal pregnancies. There was a tendency in toxemic women for increased excretion of chorionic gonadotrophin, whereas a corresponding decrease in estrogen excretion occurred in only a small proportion of cases. These combined findings were noted in only 25 per cent of the cases.

The authors suggest that if the estriol excretion curve shows a constant decline of more than 70 per cent of the previous values (60 per cent in toxemic patients), a placental insufficiency is



indicated and therapeutic decisions should be made accordingly. An absolute estriol value of lower than 3,000  $\gamma$  per 24 hours was indicative of danger for the fetus, and a titer remaining below 1,000  $\gamma$  per 24 hours indicated irreversible placental dysfunction and death of the fetus.

Robert E. L. Nesbitt, Jr.

**Acta societatis medicorum upsaliensis**

Vol. 64, 1959.

\*Odin, Lars: Studies on the Chemistry of Ovarian Cyst Contents, p. 25.

Odin: Studies on the Chemistry of Ovarian Cyst Contents, p. 25.

The contents of various ovarian cysts are subjected to extensive study by means of standard physical and biochemical determinations, paper chromatography, electrophoresis, and x-ray analysis of crystalline substances. The biochemical moieties are identified and quantitated. Included in the study are: (1) the content of 30 pseudomucinous cystadenomas including 3 associated with pseudomyxoma peritonaei, 5 peritoneal gels; (2) contents of appendiceal mucocoele; and (3) 40 specimens of serous fluid from various tumors and cysts. The carbohydrate and protein content was found to be similar to that of the blood group substances. The author points out the physical and biochemical differences between pseudomucinous cystadenomas which give rise to pseudomyxoma peritonaei and those which do not. He suggests that, whereas histological sections may not indicate the clinical course, the low fucose, high sialic acid content, and water insolubility of the former in contrast to the latter may reveal the outcome. Numerous quantitative charts and photographs of electrophoretic patterns are included in this detailed monograph.

Edward E. Wallach

**German Medical Monthly**

Vol. 4, December, 1959.

\*Rost, H. F., Paul, H., and Seeliger, H. P. R.: Repeated Miscarriages and Listeriosis, p. 124.

\*Friedberg, V.: Diuretic Treatment of Fluid Retention in Toxaemia of Pregnancy, p. 418.

Rost, Paul, and Seeliger: Repeated Miscarriages and Listeriosis, p. 124.

The authors suggest that maternal listeriosis may give rise to habitual abortion, stillbirths, and prematurity in a certain number of cases. Eight

patients are presented with poor obstetrical histories. In each case serological tests for agglutinins of *Listeria monocytogenes* were positive. All of the women were delivered of normal children following specific therapy. Treatment consisted of tetracycline, 1 Gm. daily for 7 days, followed by a sulfonamide, 4 Gm. daily for 10 days, and penicillin, 500,000 units for 3 days, during the first 2 months of pregnancy. It is suggested that therapy be repeated during the second half of gestation or when serological titers rise or complications occur. It is noteworthy that the diagnosis of listeriosis has rested solely on positive serological tests without bacteriological confirmation. No congenital malformations attributable to listeriosis have been reported; nor is there evidence that organisms are excreted in the milk of the infected mother.

Edward E. Wallach

**Friedberg: Diuretic Treatment of Fluid Retention in Toxaemia of Pregnancy, p. 418.**

The relative merits of mercurials, carbonic anhydrase, inhibitors, and chlorothiazid and its derivatives in the treatment of fluid retention in toxemia are discussed. Mercurials, with their potential danger of causing renal damage, are best used as initial therapy to induce a strong response, followed by maintenance with other diuretics. Carbonic anhydrase inhibitors are limited by their rapid diminution of effectiveness when employed without interruption. Chlorothiazide and hydrochlorothiazide have the advantages of being administrable over protracted periods, rendering antihypertensive effects and exerting no side effects on the renal tubule.

Edward E. Wallach

**Journal of the American Medical Association**

Vol. 172, Jan. 2, 1960.

Tompkins, Pendleton: Infertility Due to Faulty Intromission Successfully Treated by Prosthetic Device, p. 53.

\*Hepner, R., and Bowen, M.: The Placenta and the Fetus, p. 427.

Hepner and Bowen: Placenta and Fetus, p. 427.

The current study was conceived after the authors observed markedly aberrant growth patterns in several infants born with placentas grossly variant in structure. In a series of 654 deliveries, 262 placentas (40 per cent) showed infarcts, fibrinoid degeneration, areas of old or recent abruption, degeneration of cotyledons, loss

of large crescents of the edges, and severe malformations.

The corresponding 262 infants were compared with the 392 infants born with normal placentas. A statistically significant relationship between placental variation and growth and nutritional aspects was seen in the first 6 months of postnatal life.

The authors conclude that gross examination of the placenta may be a useful clinical tool to forewarn the physician of some common problems of the first 6 months.

John J. Dettling

### **Journal of Clinical Endocrinology and Metabolism**

Vol. 19, September, 1959.

\*Jefferies, W. M. McK., and Levy, R. P.: Treatment of Ovarian Dysfunction With Small Doses of Cortisone or Hydrocortisone, p. 1067.

**Jefferies and Levy: Treatment of Ovarian Dysfunction With Small Doses of Cortisone or Hydrocortisone, p. 1067.**

Mild hirsutism or a high level of urinary 17-ketosteroid excretion is often observed in women with functional irregularities of menstruation. Therefore, it is possible that there may be an associated mild disorder of adrenocortical function. If this were true, treatment with suitable doses of cortisone or hydrocortisone might be beneficial. Encouraging results were obtained with oral administration of either of these steroids in doses of 2.5 to 5.0 mg. at intervals of 8 hours or less to women with hirsutism and infertility. This led to an extension of the trials to include any patients with irregularity or absence of the menses on a functional basis. Among 52 such women, therapy resulted in resumption or increased regularity of ovulation in 46 (89 per cent). Of 38 patients in the series who had associated infertility, 21 (55 per cent) had one or more pregnancies while receiving this type of treatment. No untoward effects were observed. In some instances, hirsutism, acne, or chronic cystic mastitis also improved. The results suggest that an appreciable number of cases of ovarian dysfunction may be related to mild disorders of adrenocortical function and indicate that continual low-dosage adrenocortical steroid therapy is a practical and effective treatment for such patients.

J. Edward Hall

October, 1959.

\*Diczfalusy, E., Notter, G., Edsmyr, F., and Westman, A.: Transient Recurrent Gynecomastia After Removal of Estrogen-Secreting Interstitial-Cell Tumor of Testis, p. 1230.

**Diczfalusy et al.: Transient Recurrent Gynecomastia After Removal of Estrogen-Secreting Interstitial-Cell Tumor of Testis, p. 1230.**

The urinary excretion of estrone, estradiol-17B, and estriol was estimated in 96 hour specimens of urine collected from each of 17 premenopausal patients with breast cancer on 5 occasions: (1) during the first part of the menstrual cycle (follicular phase), (2) during the second part of the cycle (luteal phase), (3) 2 months after ovarian irradiation, (4) 4 months after ovarian irradiation, and (5) 2 months after bilateral oophorectomy. The greatest variation in the amount of urinary estrogen seemed to depend on ovulation and corpus luteum formation. Ovarian irradiation reduced significantly the urinary excretion of total estrogen (i.e., the sum of estrone, estradiol-17B, and estriol) below that in the follicular phase and resulted in a marked decrease in the ratio of urinary estriol to estrone and estradiol-17B. Bilateral oophorectomy, performed 5 months after ovarian irradiation, did not result in any further decrease in urinary estrogen excretion. However, the problem is complicated by the generally observed fact that the therapeutic effect of oophorectomy seems to be superior to that of ovarian irradiation.

J. Edward Hall

November, 1959.

\*Grumbach, M. M., Ducharme, J. R., and Moloshor, R. E.: Fetal Masculinizing Action of Certain Oral Progestins, p. 1369.

\*Robertson, M. E., Stiefel, M., and Laidlaw, J. C.: Influence of Estrogen on Secretion, Disposition, and Biologic Activity of Cortisol, p. 1381.

\*Smith, C. W., Jr., and Howard, R. P.: Variations in Endocrine Gland Function in Postpartum Pituitary Necrosis, p. 1420.

**Grumbach, Ducharme, and Moloshor: Fetal Masculinizing Action of Certain Oral Progestins, p. 1369.**

Data are presented on 18 females with congenital masculinization of the external genitals who were born of mothers treated with certain oral progestins during pregnancy. Nine of the mothers

had received 19-nor-17-alpha ethynyltestosterone; 1, norethynodrel; and 8 others, 17 alpha-ethynyltestosterone. The masculinizing effect on the female fetus of the first compound, and possibly the second, was comparable to that of known androgens. Labioscrotal fusion was exhibited only in those instances in which the oral progestin had been administered prior to the thirteenth week of gestation. Evidence is reviewed which suggests that these oral progestins have a direct masculinizing action on the female fetus. It suggested that the discordance in androgenic activity exhibited by these compounds in the fetus as compared to the adult may be attributed to the difference in the sensitivity of the end organs and to delayed fetal disposal of steroid transferred across the placenta. The importance of distinguishing fetal masculinization due to administration of testosterone analogues with gestational activity from those rare instances of congenital masculinization of the female fetus in which a relationship to treatment during pregnancy with progesterone or its analogues or diethylstilbestrol has been suspected but not established is emphasized. The authors recommend that treatment of pregnant women with semi-synthetic oral progestins which exhibit masculinizing properties in the female fetus be abandoned.

*J. Edward Hall*

**Robertson, Stiefel, and Laidlaw: Influence of Estrogen on Secretion, Disposition, and Biologic Activity of Cortisol, p. 1381.**

The following findings were obtained which bear on the mechanisms concerned in the rise of plasma-free 17-hydroxycorticoid levels in patients treated with estrogenic hormone.

1. Cortisol accounted for approximately 80 per cent of the plasma-free 17-OHCS in a normal subject given estrogen.
2. In patients treated with estrogenic hormone there was a marked rise in the level of plasma-free 17-OHCS but no increase in urinary total 17-OHCS excretion.
3. In a man with intact adrenals who received ACTH intravenously and in a woman with Addison's disease who received cortisol intravenously there was a greater rise in the level of plasma-free 17-OHCS and urinary F + E but a lesser rise in urinary THF + THE when estrogen was also administered.
4. On three occasions when patients with adrenal insufficiency were given cortisol intrave-

nously, estrogen produced a diminished rate of removal of free 17-OHCS from plasma and a smaller distribution volume of the injected F.

5. The pituitary glands of 3 patients who had been receiving long-term estrogen therapy showed no Crooke's changes in the basophil cells. It is concluded that the rise in level of plasma cortisol in patients receiving estrogen is due mainly to a diminished transformation of compound F to certain metabolites and to a greater retention of the hormone within the intravascular or possibly the extracellular fluid compartment. The failure of patients treated with estrogens to show evidence of an excess of cortisol is believed to be due in part to a failure of tissue levels of F to rise to the same degree as the plasma level of the hormone.

*J. Edward Hall*

**Smith and Howard: Variations in Endocrine Gland Function in Postpartum Pituitary Necrosis, p. 1420.**

Postpartum pituitary necrosis in 4 patients was manifest by classical panhypopituitarism with secondary insufficiency of the thyroid, adrenal cortex, and ovary. Three other patients presented atypical syndromes characterized by virtually normal thyroid function, variable degrees of adrenocortical insufficiency, and normal to slightly elevated urinary excretion of gonadotropin with or without the resumption of menses. Low 24 hour thyroidal I<sup>131</sup> uptakes were associated with low urinary gonadotropin levels, and normal uptakes with higher gonadotropin levels. It is inferred that in some cases of postpartum pituitary necrosis there may be decreased ACTH secretion, nearly normal TSH secretion, and restored gonadotropin secretion which, however, may not be adequate for normal ovarian function.

*J. Edward Hall*

*Vol. 20, January, 1960.*

\*Dowling, J. T., Ingbar, S. H., and Freinkel, N.: Iodine Metabolism in Hydatidiform Mole and Choriocarcinoma, p. 1.

**Dowling, Ingbar and Freinkel: Iodine Metabolism in Hydatidiform Mole and Choriocarcinoma, p. 1.**

Thyroid function and the binding of thyroxine in serum were assessed in 2 women with choriocarcinoma and 3 with hydatidiform mole. Women with choriocarcinoma who were excreting chorionic gonadotropin did not exhibit



estrogenic effects or altered binding of thyroxine by the thyroxine-binding globulin. Chorionic gonadotropin per se thus appears to play no part in the increase in serum thyroxine-binding characteristic of normal pregnancy. In women with hydatidiform moles, the production of thyroid hormone, as estimated by the thyroidal accumulation of  $I^{127}$  and concentrations of serum-bound  $I^{131}$ , protein-bound  $I^{127}$ , and butanol-extractable  $I^{131}$  reached levels found in thyrotoxicosis. These parameters returned to normal in each case after removal of the pathologic conceptus.

J. Edward Hall

#### Journal of Clinical Investigation

Vol. 38, August, 1959.

Sandberg, A. A., and Slaunwhite, W. Roy, Jr.: Transcortin: A Corticosteroid-Binding Protein of Plasma. II. Levels in Various Conditions and the Effects of Estrogens, p. 1290.

#### Journal of Dairy Science

Vol. 42, 1959.

\*Freund, M., and Murphree, R. L.: Influence of Sperm Concentration, Initial Fructose Level, and Initial Per Cent Motility on the Fructolytic Activity of Bovine Semen, p. 1320.

**Freund and Murphree: Influence of Sperm Concentration, Initial Fructose Level, and Initial Per Cent Motility on Fructolytic Activity of Bovine Semen, p. 1320.**

Three semen characteristics—sperm concentration, initial fructose level, and initial per cent motility—were measured in 262 semen specimens collected by electroejaculation from 10 Hereford bulls. Two consecutive specimens of about 5 ml. each were collected from each of the bulls 3 times a week. The fructose utilizations were determined after 20, 40, and 60 minutes of incubation at 37° C. The zero, first, and second order partial and multiple correlations were calculated from the data on total, among-bulls, and ejaculates-within-bulls bases. Each of the 3 semen characteristics, independent of the other 2 was correlated ( $P < 0.01$ ) with fructolysis, on within-bulls bases. Multiple correlations of the 3 semen characteristics with fructolysis were significant ( $P < 0.01$ ) on within-bull bases. Multiple covariance analysis showed no significant among-bull differences in fructolysis, indicating that, in this system, differences in fructose utilization may be accounted for by differences in sperm

concentration, initial fructose level, and initial per cent motility.

M. J. Fitzpatrick

#### Lancet

Vol. 2, Nov. 7, 1959.

\*Galton, Michael, and Benirschke, Kurt: Forty-six Chromosomes in an Ovarian Teratoma, p. 761.

**Galton and Benirschke: Forty-six Chromosomes in an Ovarian Teratoma, p. 761.**

The tissue for this study was obtained at the third operation on a recurrent, solid, well-differentiated teratoma in a 24-year-old woman whose original tumor in the left ovary followed her only pregnancy 2 years previously. Explants from a solid metastasis to the colon were successfully cultured and treated with colchicine. About 100 squashed cells in metaphase, all obviously diploid, were seen. Four had good chromosome separation and in each instance numbered 46. This suggests a normal female distribution with the XX allelomorph. This study does not furnish the answer to the origin of teratomas. Similar studies of teratoma in males will be necessary.

David M. Kydd

Nov. 14, 1959.

\*Dawkins, M. J. R., MacGregor, W. G., and McLean, A. E. M.: The Detection of Placental Degeneration During Pregnancy Serum-Isocitric-Dehydrogenase Activity, p. 827.

**Dawkins, MacGregor, and McLean: Detection of Placental Degeneration During Pregnancy Serum-Isocitric-Dehydrogenase Activity, p. 827.**

In this preliminary report the isocitric dehydrogenase (ICD) activity in the serum of 12 normal pregnant women was found to be  $1.7 \pm 6$  units. In 8 instances of pre-eclamptic toxemia the following values were obtained: 1.0, 2.4, 5.0, 5.3, 6.6, 8.3, 10.3, and 18.0 units. The fact that not all of these latter values were beyond the normal range was ascribed to the belief that the enzyme is liberated only from dying cells and therefore an increase in the serum ICD activity indicates only recent degeneration of the placenta (probably within 48 hours). Continued elevation of serum ICD activity may indicate progressive placental degeneration. Further work is in progress to more clearly define the usefulness of this test.

David M. Kydd



Nov. 28, 1959.

\*Wilson, F., and Sedzimir, C. B.: Hypothermia and Hypotension During Craniotomy in a Pregnant Woman, p. 947.

**Wilson and Sedzimir: Hypothermia and Hypotension During Craniotomy in a Pregnant Woman, p. 947.**

A multiparous woman when 32 weeks pregnant had hemorrhage from an intracranial aneurysm which necessitated urgent craniotomy under hypothermia and hypotension. The patient was anesthetized by sodium thiopentone, followed by suxamethonium chloride for relaxation, and maintained with nitrous oxide, oxygen, and ether. She was cooled by means of ice until her temperature reached 30° C. During the cooling the fetal heart rate dropped constantly with the maternal temperature. At first the uterus appeared fairly flaccid. During the operation hemorrhage was encountered and trimethaphan was administered until the maternal blood pres-

sure reached 40/25. The maternal pulse rate rose to 95 but the fetal heart rate dropped further to 85. The uterus was now stony hard. The aneurysm was clipped and the operation finished without complication. The maternal blood pressure slowly rose. With the rise in blood pressure the fetal heart rate rose to 100. The uterus remained hard and the fetus was extremely active. The day following the operation labor began and a normal child was delivered some 4 hours later. The patient's postoperative and postpartum progress was entirely uneventful. The uterine hypertonicity and excessive fetal movements during the period of hypothermia and hypotension are difficult to explain. Anoxia seems to the authors to be unlikely. Labor itself did not begin until 29 hours after the operation. Despite these rigors a normal infant was delivered, and the infant has appeared to be entirely well since the procedure.

*David M. Kydd*

## Correspondence

### **Interstitial and intrauterine pregnancy**

*To the Editors:*

On reading through the February, 1960, issue of the JOURNAL, I came across an account of a "Coexistent Interstitial and Intrauterine Pregnancy Following Homolateral Salpingo-oophorectomy," by Basil V. Bisca and Martin E. Felder, on page 263.

Since the authors make the daring claim at the end of the introduction that "the literature shows no similar case," I thought I might acquaint you with an almost identical case which I published in *The Proceedings of the Royal Society of Medicine Section of Obstetrics and Gynecology*, Volume 29, page 471, May, 1936.

95, Harley Street  
London, W.1, England  
March 10, 1960

C. Keith Vartan

### **Reply by Dr. Bisca**

*To the Editors:*

I appreciate Mr. Vartan's communication calling attention to my oversight and including an implied bit of sage advice that may save me from worse future embarrassment. Next time, thanks to him, I'll cover myself by saying: "I failed to find a similar case in the literature."

These reminders are probably especially helpful for those who may be interested in the subject sufficiently to pursue it further in the literature. To them I can recommend Mr. Vartan's enjoyable case report.

My personal chagrin is alleviated in a minute degree by the thought that my own report was so carefully read by someone so far away.

2265 North High St.  
Columbus 1, Ohio  
April 13, 1960

Basil V. Bisca, M.D.

## Items

### American Board of Obstetrics and Gynecology

Applications for certification in the American Board of Obstetrics and Gynecology, new and reopened, Part I, and requests for re-examination in Part II are now being accepted. All candidates are urged to make such application at the earliest possible date. Deadline for receipt of applications is Aug. 1, 1960. No applications can be accepted after that date.

The following change in requirements for certification was made by the members of the American Board of Obstetrics and Gynecology at the recent annual meeting in Chicago.

"A Resolution was passed at the recent annual meeting of this Board which eliminates the sub-

mission of Case Reports as part of the Part I Examination. It is required, however, that each candidate eligible to take the Part II Examination bring to the place of examination, a duplicate list of Hospital Admissions as submitted with his or her application. *This change in requirements is not retroactive and therefore applies to candidates making application for the 1961 examinations.*"

It has also been resolved by members of the Board that Applications for Appraisal of Incomplete Training will no longer be accepted for review by the Residency Review Committee.

Robert L. Faulkner, M.D., Secretary  
2105 Adelbert Road  
Cleveland 6, Ohio

### Program of sessions devoted to gynecology and obstetrics at the Clinical Congress of the American College of Surgeons, San Francisco, Oct. 10-14, 1960

Monday, October 10  
8:30-11:30 A.M.

Postgraduate Course, Chairman, George E. Judd,  
Los Angeles

*Preoperative, Operative, and Postoperative Complications and Treatment of the Gynecological Surgical Patient*, Harold K. Marshall, M.D., F.A.C.S., Glendale, California, Moderator

Preoperative Examination and Preparation, J. G. Moore, M.D., Los Angeles

Emotional Preparation of the Surgical Patient, Allan C. Barnes, M.D., F.A.C.S., Baltimore

Anesthesia, John B. Dillon, M.D., Los Angeles

Coagulation Defects, Operative and Postoperative, Louis J. Lombardo, Jr., M.D., Los Angeles

Bowel Preparation, Complications, and Management, Alan P. Thal, M.D., Minneapolis

1:30-5:00 P.M.

#### Panel Discussions

1:30-3:00: *Current Therapy of Toxemias of Pregnancy*

Moderator, T. N. Evans, M.D., F.A.C.S., Ann Arbor

Panel, Charles A. Hunter, Jr., M.D., F.A.C.S., Indianapolis; Ernest W. Page, M.D., San Francisco; Gordon W. Douglas, M.D., F.A.C.S., New York

3:30-5:00: *Carcinoma of the Endometrium*

Moderator, Saul B. Gusberg, M.D., F.A.C.S., New York

Panel, Charles E. McLennan, M.D., San Francisco; Joe V. Meigs, M.D., F.A.C.S., Boston; James F. Nolan, M.D., F.A.C.S., Los Angeles

Tuesday, October 11  
8:30-11:30 A.M.

Postgraduate Course, Chairman, George E. Judd,  
Los Angeles

*Preoperative, Operative, and Postoperative Complications and Treatment of the Gynecological Surgical Patient*, J. Howard Payne, M.D., F.A.C.S., Los Angeles, Moderator

Shock Mechanisms and Treatment, Leonard Rosoff, M.D., F.A.C.S., Los Angeles

Pulmonary Complications, Joseph Boyle, M.D.,  
Los Angeles  
Acute Renal Failure, Allan G. Redeker, M.D.,  
Los Angeles  
Thrombophlebitis, Frank H. Leeds, M.D.,  
F.A.C.S., San Francisco  
Cardiac Arrest, William P. Mikkelsen, M.D.,  
F.A.C.S., Los Angeles

1:30-5:00 P.M.

**Panel Discussions**

1:30-3:00: *Changing Aspects of Therapeutic Abortion*

Moderator, Keith P. Russell, M.D., F.A.C.S., Los Angeles

Panel, Ralph J. Gampell, M.D., Los Altos, California; C. Paul Hodgkinson, M.D., F.A.C.S., Detroit; Frank R. Lock, M.D., F.A.C.S., Winston-Salem; Wesley T. Pommerenke, M.D., F.A.C.S., Rochester, New York

3:30-5:00: *Control of Conception*

Moderator, Charles S. Stevenson, M.D., F.A.C.S., Detroit

Panel, Celso-Ramón García, M.D., Brookline, Massachusetts; Edward T. Tyler, M.D., Los Angeles; Robert B. Wilson, M.D., F.A.C.S., Rochester, Minnesota

Wednesday, October 12

8:30-11:30 A.M.

**Postgraduate Course**, Chairman, George E. Judd, Los Angeles

*Glandular Epithelium of the Uterus*, James F. Nolan, M.D., F.A.C.S., Los Angeles, Moderator

*Embryology and Histology of Endocervix and Endometrium*, C. Frederic Fluhmann, M.D., San Francisco

*Relationship of Uterine Bleeding to Endometrial Histology*, Richard L. Taw, M.D., Los Angeles  
*Adenoacanthoma*, Edward G. Jones, M.D., F.A.C.S., Pomona, California

*Adenocarcinoma of the Endocervix*, William O. Thomas, Jr., M.D., F.A.C.S., Portland, Oregon

*Adenocarcinoma of the Endometrium*, Saul B. Gusberg, M.D., F.A.C.S., New York

1:30-5:00 P.M.

**Forum on Gynecological and Obstetrical Research** (Program to be selected and announced)  
Chairman, Milton L. McCall, M.D., F.A.C.S.,

Pittsburgh, and Somers H. Sturgis, M.D., F.A.C.S., Boston

Thursday, October 13

8:30-11:30 A.M.

**Postgraduate Course**, Chairman, George E. Judd, Los Angeles

*Uterine Muscle Physiology and Function*, Ralph C. Benson, M.D., F.A.C.S., Portland, Oregon, Moderator

*Uterine Muscle Reactions (Studies with Miniature Balloon)*, Roberto Caldeyro-Barcia, M.D., Montevideo, Uruguay

*Uterine Muscle Reactions (Studies with Muscle Strips)*, Harry S. McGaughey, Jr., M.D., Charlottesville, Virginia

*The Use of Relaxin in Labor*, William G. Slate, M.B., Ch.B., Chicago

*Induction of Labor*, Bernard J. Hanley, M.D., F.A.C.S., Los Angeles

*Hazards and Contraindications of Induction of Labor*, Harry Fields, M.D., F.A.C.S., Philadelphia

1:30-3:00 P.M.

**Panel Discussions**

1:30-3:00: *Hydatid Mole and Choriocarcinoma*

Moderator, John I. Brewer, M.D., F.A.C.S., Chicago

Panel, Philip H. Arnot, M.D., F.A.C.S., San Francisco; Leon P. Fox, M.D., F.A.C.S., San Jose, California; Frederick J. Hofmeister, M.D., F.A.C.S., Milwaukee

Friday, October 14

8:30-11:30 A.M.

**Symposium**, Moderator, Harry M. Nelson, M.D., F.A.C.S., Detroit

1. *Inefficiency of Relaxin for Arresting or Facilitating Labor*, Roberto Caldeyro-Barcia, M.D., Montevideo, Uruguay

2. *Clinical Evaluation of Relaxin for Arresting or Facilitating Labor*, Ralph A. Reis, M.D., F.A.C.S., Chicago

3. *Ten-Year End Results, Surgical Treatment of Carcinoma of the Cervix*, Joe V. Meigs, M.D., F.A.C.S., Boston

4. *Ten-Year End Results, Radiological Treatment of Carcinoma of the Cervix*, Hans-Ludvig Kottmeier, M.D., F.A.C.S. (Hon.), Stockholm, Sweden



1:30-4:45 P.M.

**Panel Discussions**

1:30-3:00: *Shock and Shock-like Reactions*

Moderator, Emil J. Krahulik, M.D., F.A.C.S.,  
Los Angeles

Panel, Milton J. Marmer, M.D., Beverly Hills,  
California; David State, M.D., F.A.C.S., New  
York; John R. Upton, M.D., F.A.C.S., San  
Francisco; Howard E. Snyder, M.D., F.A.C.S.,  
Winfield, Kansas

3:15-4:45: *Vaginal Approach to Pelvic Surgery*  
Moderator, Eugene A. Edwards, M.D., F.A.C.S.,  
Chicago

Panel, *Colpotomy*, William C. Bradbury, M.D.,  
F.A.C.S., Santa Monica, California; *Vaginal*  
*Hysterectomy*, Harry Boysen, M.D., F.A.C.S.,  
Chicago; *Manchester Operation*, John B.  
Montgomery, M.D., F.A.C.S., Philadelphia;  
*Schauta Operation*, Milton L. McCall, M.D.,  
F.A.C.S., Pittsburgh

# Roster of American obstetrical and gynecological societies\*

(Appears in January and July)

**American College of Obstetricians and Gynecologists.** (1951) *President*, C. Paul Hodgkinson. *Secretary*, Craig W. Muckle, 1806 Garrett Rd., Lansdowne, Pa. Next meeting, April 21-28, 1961, Americana, Bal Harbour, Fla.

**American Gynecological Society.** (1876) *President*, Karl H. Martzloff. *Secretary*, Andrew A. Marchetti, 3800 Reservoir Rd., Washington 7, D. C.

**American Association of Obstetricians and Gynecologists.** (1888) *President*, Robert A. Ross, Chapel Hill, N. C. *Secretary*, Clyde L. Randall, 216 Summer St., Buffalo 22, N. Y. Meetings, Sept. 8-10, 1960, and March 11-12, 1961.

**Central Association of Obstetricians and Gynecologists.** (1929) *President*, Isadore Dyer, New Orleans, La. *Secretary*, Herman L. Gardner, 633 Hermann Professional Bldg., Houston 25, Texas. Annual meeting, Hotel Muehlebach, Kansas City, Mo., Oct. 6-8, 1960.

**Akron Obstetrical and Gynecological Society.** (1946) *President*, Carl J. Paternite. *Secretary*, Edson A. Freeman, 2032 Chestnut Blvd., Cuyahoga Falls, Ohio. Meetings, third Friday, January, April, June, and October.

**Alabama Association of Obstetricians and Gynecologists.** (1940) *President*, O. M. Otts, Jr. *Secretary*, Theo F. Middleton, 1302 Government St., Mobile, Ala. Meetings, April and October.

**Alameda County Gynecological Society.** (1951) *President*, Samuel P. Hall. *Secretary*, Samuel C. Iwig, 1300 Bancroft Ave., San Leandro,

**South Atlantic Association of Obstetricians and Gynecologists.** (1938) *President*, John B. Cross. *Secretary*, Laurence L. Hester, Jr., Medical College of South Carolina, Charleston, S. C. Next meeting Feb. 15-18, 1961, Biltmore Hotel, Atlanta, Ga.

**A. M. A. Section on Obstetrics and Gynecology.** (1859) *Chairman*, Curtis J. Lund, Rochester, N. Y. *Secretary*, Keith P. Russell, 511 S. Bonnie Brae St., Los Angeles 57, Calif. Next meeting, June 26-30, 1961, New York, N. Y.

**Society of Obstetricians and Gynaecologists of Canada.** (1944) *President*, D. E. Cannell. *Secretary*, F. P. McInnis, 280 Bloor St., W., Toronto 5. Annual meeting, The Chantecler, Ste. Adele en haut, Que., June 15-18, 1961.

**American Board of Obstetrics and Gynecology, Inc.** (1930) *President*, F. Bayard Carter. *Secretary*, Robert L. Faulkner, 2105 Adelbert Rd., Cleveland 6. Next meeting April 7-14, 1961.

Calif. Meetings, fourth Wednesday, September through June.

**Arkansas Obstetrical and Gynecological Society.** (1953) *President*, James D. Mashburn. *Secretary*, Ruth Lesh, 221 N. College, Fayetteville, Ark. Meetings, spring and fall.

**Atlanta Obstetrical and Gynecological Society.** (1954) *President*, Emmett Durham Colvin. *Secretary*, Stephen T. Barnett, Jr., 478 Peachtree St., N.E., Atlanta, Ga. Meetings, October, February, April, and June.

**Birmingham Obstetrical and Gynecological Society.** (1949) *President*, Wade Cline. *Secretary*, George C. Douglas, 1923 14th Ave., S., Birmingham, Ala. Four called meetings yearly.

**Boston, Obstetrical Society of.** (1861) *President*, John L. Newell. *Secretary*, Luke Gillespie, 221 Longwood Ave., Boston 15, Mass. Meetings, third Monday, January, February, March, April, October, and November.

\*Changes, omissions, and corrections must be received by the publisher two months in advance, by May 1 for the July Roster and by November 1 for the January Roster. Please address The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Missouri. The number after the Society's name is the year of founding. For further information, address the respective secretaries.

**Bronx Gynecological and Obstetrical Society.**

(1924) *President*, A. Charles Posner. *Secretary*, William J. Farrell, 2980 Valentine Ave., Bronx 58, N. Y. Meetings, fourth Monday, October through May.

**Brooklyn Gynecological Society, Inc. (1890)**

*President*, Louis M. Hellman. *Secretary*, Warren A. Lapp, 731 E. 22nd St., Brooklyn 10, N. Y. Meetings, third Wednesday, January, February, March, April, May, October, and November.

**Buffalo Obstetrical and Gynecological Society.**

(1946) *President*, Chester J. Kaminski. *Secretary*, Milford Childs, 2900 Main St., Buffalo 14, N. Y. Meetings, first Tuesday, September through May.

**Central New York Association of Gynecologists and Obstetricians. (1938)**

*President*, Vincent J. Hemmer. *Secretary*, James N. Capps, 325 University Ave., Syracuse 10, N. Y. Meetings, first Tuesday, September, November, January, March, and May.

**Chicago Gynecological Society. (1878)**

*President*, Clyde J. Geiger. *Secretary*, William G. Cummings, 636 Church St., Evanston, Ill. Meetings, third Friday, October through June.

**Cincinnati Obstetrical and Gynecological Society.**

(1876) *President*, Richard T. F. Schmidt. *Secretary*, Arthur G. King, 199 William Howard Taft Rd., Cincinnati 19, Ohio. Meetings, third Thursday, monthly.

**Cleveland Society of Obstetrics and Gynecology.**

(1947) *President*, Eduard Eichner. *Secretary*, Richard Glove, 3550 Warrensville Center Rd., Shaker Heights 22, Ohio. Meetings, fourth Monday, September, November, January, March, and May.

**Columbus Obstetrical and Gynecological Society.**

(1944) *President*, Harry E. Ezell. *Secretary*, Wm. E. Copeland, Ohio State University Hospital, Columbus, Ohio. Meetings, fourth Wednesday of month, October through June.

**Connecticut Society of American Board Obstetricians and Gynecologists, Inc. (1952)**

*President*, A. Rocke Robertson. *Secretary*, Robert H. Wyatt, 54 Lafayette Place, Stamford, Conn.

**Dallas-Fort Worth Gynecologic and Obstetric Society. (1948)**

*President*, T. D. Mayo. *Secretary*, James T. Downs, III, 3707 Gaston Ave., Dallas 10, Texas. Meetings, spring and fall.

**Dayton Obstetrical and Gynecological Society.**

(1937) *President*, Nicholas J. Thompson. *Secretary*, Wm. Dietrichson, 252 Talbott Bldg., Dayton, Ohio. Meetings, third Wednesday each month, September through May.

**Denver Gynecological and Obstetrical Society.**

(1942) *President*, Raymond C. Chatfield. *Secretary*, George M. Horner, 3705 E. Colfax Ave., Denver 6, Colo. Meetings, first Monday of every month.

**Florida Obstetric and Gynecologic Society.**

(1948) *President*, Homer L. Pearson, Jr. *Secretary*, Sam W. Denham, 1661 Riverside Ave., Suite A., Jacksonville 4, Fla. Next meeting, December, 1960.

**Georgia State Obstetrical and Gynecological Society. (1951)**

*President*, Wm. Jordan. *Secretary*, C. I. Bryans, Jr., 1139 Druid Park Ave., Augusta, Ga. Meetings, spring and fall.

**Harris, John Warton, Obstetrical Society. (1953)**

*President*, William V. Luetke. *Joint Secretaries*, Madeline Thornton and William Keikhofer, State of Wisconsin General Hospital, 1300 University Ave., Madison, Wis. Annual meeting in May.

**Honolulu Obstetrical and Gynecological Society.**

(1947) *President*, Richard Sakimoto. *Secretary*, John Ohtani, Rm. 410, Professional Center Bldg., 1481 S. King St., Honolulu 14, Hawaii. Meetings, third Monday of each month, Mabel Smythe Bldg.

**Houston Gynecological and Obstetrical Society.**

(1956) *President*, Seward H. Wills. *Secretary*, Mary Ann McKinney, 5000 Montrose Blvd., Houston 6, Texas. Meetings quarterly.

**Indiana Obstetrical and Gynecological Society.**

(1947) *President*, David Bickel. *Secretary*, Floyd T. Romberger, Jr., 3440 N. Meridian St., Indianapolis 8, Ind. Meetings, January and May.

**Interurban Obstetrical and Gynecological Society. (1949)**

*President*, Milton Potter. *Secretary*, E. R. Duggan, 1351 Mt. Hope Ave., Rochester 20, N. Y. Meeting, October, 1960.

**Iowa Obstetrical and Gynecological Society.**

(1947) *President*, Walter J. Balzer. *Secretary*, Clifford P. Goplerud, State University of Iowa Hospitals, Iowa City, Iowa. Meetings, November, 1960, and January, 1961.

**Jacksonville Obstetrical and Gynecological Society. (1960)**

*President*, John J. Fisher. *Secretary*, Doris N. Carson, 836 Miami Rd., Jacksonville, Fla. Meetings, quarterly.

**Kansas City Gynecological Society. (1922)**

*President*, Kenneth Nicolay. *Secretary*, Joseph Williams, 425 East 63rd St., Kansas City, Mo. Meetings, September, November, January, March, and May.

**Kentucky Obstetrical and Gynecological Society.**

(1947) *President*, Robert Monroe. *Secretary*,

- Douglas M. Haynes, 323 Chestnut St., Louisville, Ky. Annual meeting in the spring.
- Long Beach Obstetrical and Gynecological Society.** (1954) *President*, Keith C. White. *Secretary*, A. F. Forster, 3019 Bellflower, Long Beach, Calif. Meetings, third Tuesday, September, November, January, March, and May.
- Los Angeles Obstetrical and Gynecological Society, Inc.** (1914) *President*, John L. Gaspar. *Secretary*, Keith P. Russell, 5478 Wilshire Blvd., Room 222, Los Angeles 36, Calif. Meetings, second Tuesday, September, November, January, March, and May.
- Louisville Obstetrical and Gynecological Society.** (1923) *President*, W. P. Eubank. *Secretary*, Edward Bell, 1169 Eastern Parkway, Louisville 17, Ky. Meetings, fourth Monday, September, October, November, January, February, March, April, and May.
- Madison Obstetrical and Gynecological Society.** (1950) *President and Secretary*, John Healy, Gorham St., Madison, Wis. Meetings, first Tuesday each month.
- Maryland Obstetrical and Gynecological Society.** (1929) *President*, William Stephens. *Secretary*, D. Frank Kaltreider, University Hospital, Lockwood and Greene Sts., Baltimore, Md. Meetings, first Thursday, September, November, January, March, and May.
- Memphis Obstetrical and Gynecological Society.** (1950) *President*, Glenn H. Williams. *Secretary*, Charles R. Riggs, 166 N. Bellevue, Memphis, Tenn. Meetings, second Tuesday, October through May.
- Miami Obstetrical and Gynecological Society.** (1946) *President*, J. Robert Sory. *Secretary*, Norman McLeod, 249 Sevilla Ave., Coral Gables, Fla. Meetings, second Thursday, January, March, May, and November.
- Michigan Society of Obstetricians and Gynecologists.** (1924) *President*, James H. Beaton. *Secretary*, Robert G. Swanson, 314 Eastland Center Professional Bldg., Detroit 36, Mich. Meetings, Sept. 28 and Dec. 6, 1960; February, April, and May, 1961.
- Milwaukee Gynecological Society.** (1951) *President*, John W. R. Thoma. *Secretary-treasurer*, Lester H. Verch, 411 E. Mason St., Milwaukee 2, Wis. Meetings, last Monday, November, January, March, and April.
- Minneapolis Obstetrical and Gynecological Society.** (1955) *President*, Maxwell Barr. *Secretary*, Richard R. Fliehr, 301 Doctors Bldg., Minneapolis 2. Meetings, four times a year.
- Minnesota Obstetrical and Gynecological Society.** (1936) *President*, Edward A. Banner. *Secretary*, Alex Barno, 4959 Excelsior Blvd., Minneapolis 16, Minn. Meetings, spring and fall.
- Mississippi Obstetrical and Gynecological Society.** (1947) *President*, Carl Lewis. *Secretary*, Blanche Lockard, 838 Lakeland Drive, Jackson, Miss. Meetings, May and November.
- Mobile County Obstetrical and Gynecological Society.** (1949) *President*, N. L. Brown. *Secretary*, John F. Vanhoof, 1367 Government St., Mobile, Ala. Meetings, second Wednesday every third month.
- Montana State Obstetrical and Gynecological Society.** (1946) *President*, Richard L. Peterson. *Secretary*, Joseph H. Brancamp, Mayer Bldg., 10 S. Idaho, Butte, Mont. Next meeting, May, 1961.
- Nashville Obstetrical and Gynecological Society.** (1955) *President*, Edwin L. Williams. *Secretary*, B. K. Hibbett, III, 2122 West End Ave., Nashville 5, Tenn. Meetings, first Tuesday in January, April, July, and October.
- Nassau Obstetrical and Gynecological Society.** (1944) *President*, Francis D. Maloney. *Secretary*, William H. Murphy, 15 Clinton Ave., Rockville Center, N. Y. Meetings, third Monday, September, November, February, and May.
- New England Obstetrical and Gynecological Society.** (1929) *President*, Clyde Swett, Island Falls, Maine. *Secretary*, William A. Lynch, 1101 Beacon St., Brookline 46, Mass. Next meeting, Nov. 2, 1960, at Boston.
- New Haven Obstetrical Society.** (1946) *President*, Irving Friedman. *Secretary*, Edward Day, 610 Campbell Ave., West Haven, Conn. Meetings, third Tuesday, September, November, January, March, and May.
- New Jersey Obstetrical and Gynecological Society.** (1947) *President*, Harold Schwartz. *Secretary*, Christopher T. Reilly, 530 N. Maple Ave., Ridgwood, N. J. Meetings, April and October.
- New Mexico Obstetrical and Gynecological Society.** (1947) *President*, Howard L. Smith. *Secretary*, Henry R. Hyslop, 313 W. Country Club Rd., Roswell, N. Mex. Meetings, quarterly.
- New Orleans Gynecological and Obstetrical Society.** (1924) *President*, Daniel W. Beacham. *Secretary*, Frank Nix, 1407 S. Carrollton Ave., New Orleans, La. Meetings, October, November, January, March, and May.



- New York Obstetrical Society.** (1863) *President*, Carl T. Javert. *Secretary*, Saul B. Gusberg, 180 Fort Washington Ave., New York 32, N. Y. Meetings, second Tuesday, September through May.
- North Carolina Obstetrical and Gynecological Society.** (1932) *President*, James A. Crawell. *Secretary*, Kenneth A. Podger, Durham Surgical Clinic, Durham, N. C.
- North Dakota Society of Obstetrics and Gynecology.** (1938) *President*, James H. Mahoney. *Secretary*, G. Wilson Hunter, Fargo Clinic, Fargo, N. D. Meetings, Sept. 9, 10, 1960; May, 1961.
- Northeastern New York Obstetrical and Gynecological Society.** (1935) *President*, James H. Flynn. *Secretary*, D. F. O'Keeffe, 153 Bay St., Glens Falls, N. Y. Meetings, fourth Thursday, January, April, and September.
- Northern California Obstetrical and Gynecological Society.** (1955) *President*, Warren E. Jones. *Secretary*, Andrew M. Henderson, Jr., 2901 Capitol Ave., Sacramento, Calif. Meetings, January, April, July, and October.
- Oklahoma City Obstetrical and Gynecological Society.** (1940) *President*, Milton Serwer. *Secretary*, Charles D. Bodine, 1220 N. Walker, Oklahoma City, Okla. Meetings, third Wednesday each month.
- Omaha Obstetrical and Gynecological Society.** (1947) *President*, Walter J. Holden. *Secretary*, William Boelter, 525 Doctors Bldg., Omaha, Neb. Meetings, third Wednesday, January, March, May, September, and November.
- Oregon Society of Obstetricians and Gynecologists.** (1946) *President*, John Kirk. *Secretary*, Richard Franklin, 6815 S.W. 11th Dr., Portland 19, Ore. Meetings, third Friday, October through May, except December.
- Pacific Coast Obstetrical and Gynecological Society.** (1931) *President*, George Judd, Los Angeles. *Secretary*, Keith Russell, 511 S. Bonnie Brae St., Los Angeles 57, Calif. Meeting, Sept. 28-Oct. 1, 1960.
- Pacific Northwest Obstetrical and Gynecological Association.** (1947) *President*, Duncan R. Neilson. *Secretary*, Clifford L. Fearl, 1133 S.W. Market St., Portland 1, Ore. Next meeting, Gearhart, Ore., June 18-20, 1961.
- Philadelphia, Obstetrical Society of.** (1868) *President*, J. Edward Lynch. *Secretary*, George C. Lewis, Jr., 133 S. 36th St., Philadelphia 4, Pa. Meetings, first Thursday, October through May.
- Phoenix Obstetrical and Gynecological Society.** (1959) *President*, Clarence Warrenburg. *Secretary*, William D. Lawrence, 1313 N. Second St., Phoenix, Ariz. Meetings, January, March, May, September, and November.
- Pittsburgh Obstetrical and Gynecological Society.** (1934) *President*, Joseph Longhrey. *Secretary*, Dean Shannon, 405-B First Federal Plaza, New Castle, Pa. Meetings, first Monday, October through May.
- Portland Society of Obstetricians and Gynecologists.** (1928) *President*, Ronald P. Neilson. *Secretary*, W. O. Thomas, Jr., 1735 N. Wheeler Ave., Portland, Ore. Meetings, fourth Wednesday, September through May.
- Queens Gynecological Society.** (1948) *President*, Max Friedman. *Secretary*, B. Edmond Thomas, 30 Grace Ave., Great Neck, N. Y. Meetings, second Wednesday, October, December, February, and April.
- Rochester Obstetrical and Gynecological Society.** (1939) *President*, Edward Callahan. *Secretary*, George C. Trombetta, 16 N. Goodman St., Rochester 7, N. Y.
- St. Louis Gynecological Society.** (1924) *President*, Roy V. Boedeker. *Secretary*, Bryce H. Bondurant, 950 Francis Place, Clayton, Mo. Meetings, Oct. 13, Dec. 8, 1960; Feb. 9, April 13, 1961.
- San Antonio Obstetrical and Gynecological Society.** *President*, G. G. Passmore. *Secretary*, Frank M. Posey, Jr., 101 N. McCollough, San Antonio, Texas.
- San Diego Gynecological Society.** (1937) *President*, George R. Turner. *Secretary*, Francis L. Rook, 3650 Clairmont Dr., San Diego 17, Calif. Meetings, called by Council.
- San Francisco Gynecological Society.** (1929) *President*, Edmund Overstreet. *Secretary*, Carl Goetsch, 2915 Telegraph Ave., Berkeley 5, Calif. Meetings, second Friday, October through May, except December.
- Seattle Gynecological Society.** (1941) *President*, R. N. Rutherford. *Secretary*, Walter Keifer, 1145 Broadway, Seattle, Wash. Meetings, third Wednesday, September, October, November, January, March, and April.
- South Carolina Obstetrical and Gynecological Society.** (1946) *President*, David F. Watson. *Secretary*, Albert J. Baroody, 352 W. Palmetto St., Florence, S. C. Next meeting, October, 1960.
- South Dakota Society of Obstetrics and Gynecology.** (1952) *President*, H. Benjamin Mun-

son. *Secretary*, H. H. Theissen, 728 Columbus St., Rapid City, S. D. Meetings, May and September.

**Southeastern Obstetrical and Gynecological Society.** *President*, John R. McCain. *Secretary*, T. Bert Fletcher, Jr., P.O. Box 3488, MSS, 1203 Miccosukee Rd., Tallahassee, Fla. Meeting, spring.

**Southern California, Obstetrical and Gynecological Assembly of.** (1945) *President*, Keith P. Russell. *Secretary*, Leon K. Shulman, 435 N. Rosbury Dr., Beverly Hills, Calif. Next meeting, Los Angeles, Feb. 13-17, 1961.

**Southwest Obstetrical and Gynecological Society.** (1951) *President*, Charles Newcomb. *Secretary*, Zeph. B. Campbell, 550 W. Thomas Rd., Phoenix, Ariz. Next meeting, Las Vegas, Nev., Nov. 6-8, 1960.

**Tennessee State Obstetrical and Gynecological Society.** *President*, Homer Pace. *Secretary*, J. W. Ellis, 2122 W. End Ave., Nashville 5, Tenn. Meetings, yearly in April.

**Texas Association of Obstetricians and Gynecologists.** (1930) *President*, Oran Presean. *Secretary*, Hugh W. Savage, 815 Fifth Ave., Ft. Worth, Texas. Annual meeting, Feb. 17-18, 1961.

**Tulsa Obstetrical and Gynecological Society.** (1955) *President*, William F. Thomas, Jr. *Secretary*, Robert E. Dillman, 2021 S. Lewis Ave., Tulsa 4, Okla. Meetings, second Wednesday, September and November.

**Tucson Obstetrical and Gynecological Society.** (1954) *President*, C. J. Newcomb. *Secretary*,

H. G. Carstensen, Craycroft Medical Center, Suite 404, Tucson, Ariz. Meetings, second Monday, September through May.

**Utah Obstetrical and Gynecological Society.** (1948) *President*, W. J. Jones. *Secretary*, E. Conrad Monson, 2955 Harrison Blvd., Ogden, Utah. Meetings, September, December, February, and May.

**Virginia Obstetrical and Gynecological Society.** (1936) *President*, William D. Suggs. *Secretary*, Brock D. Jones, Jr., 1204 Colonial Ave., Norfolk 17, Va. Meetings, spring and fall.

**Washington Gynecological Society.** (1933) *President*, George Ellis. *Secretary*, Jed Pearson, 1834 K. St., N.W., Washington, D. C. Meetings, January, March, and May.

**Washington State Obstetrical Association.** (1936) *President*, Fredric Balz. *Secretary*, Carter A. Swanson, 1120 Cherry St., Seattle 4, Wash. Next meeting, Oct. 22, 1960.

**West Texas Obstetrical and Gynecological Society.** (1954) *President*, R. Lee Rode. *Secretary*, H. Ray Buzbee, 1101 N. 19th St., Abilene, Texas. Meeting, November, 1961.

**Westchester Obstetrical and Gynecological Society.** (1939) *President*, Edwin A. Haverty. *Secretary*, Norman M. Weinrod, 175 Crary Ave., Mt. Vernon, N. Y.

**Wisconsin Society of Obstetrics and Gynecology.** (1940) *President*, David Werner, Milwaukee, Wis. *Secretary*, John J. Boersma, 306 Cherry St., Green Bay, Wis. Meetings, May and October.



*just pour powder  
from  
one packet*

•  
each packet  
is equivalent to  
one rounded teaspoonful  
of Metamucil powder

•  
all the advantages  
of smoothage therapy  
in the relief and  
correction of constipation

it's new  
**INSTANT MIX  
METAMUCIL**

*add cool water  
slowly  
...it's instantly  
mixed*

•  
stimulates normal  
peristalsis

•  
keeps stools soft and  
easy to pass

•  
induces natural elimination

•  
promotes regularity

•  
avoids harsh laxatives  
or purgatives

it's new  
**INSTANT MIX  
METAMUCIL**

**Rx**

*Instant Mix Metamucil  
Carton of 16 or 30 packets.  
Sig: usual adult dose  
is one packet,  
one to three times  
daily; children less,  
according to age.*

*convenient,  
premeasured-  
dose packets*

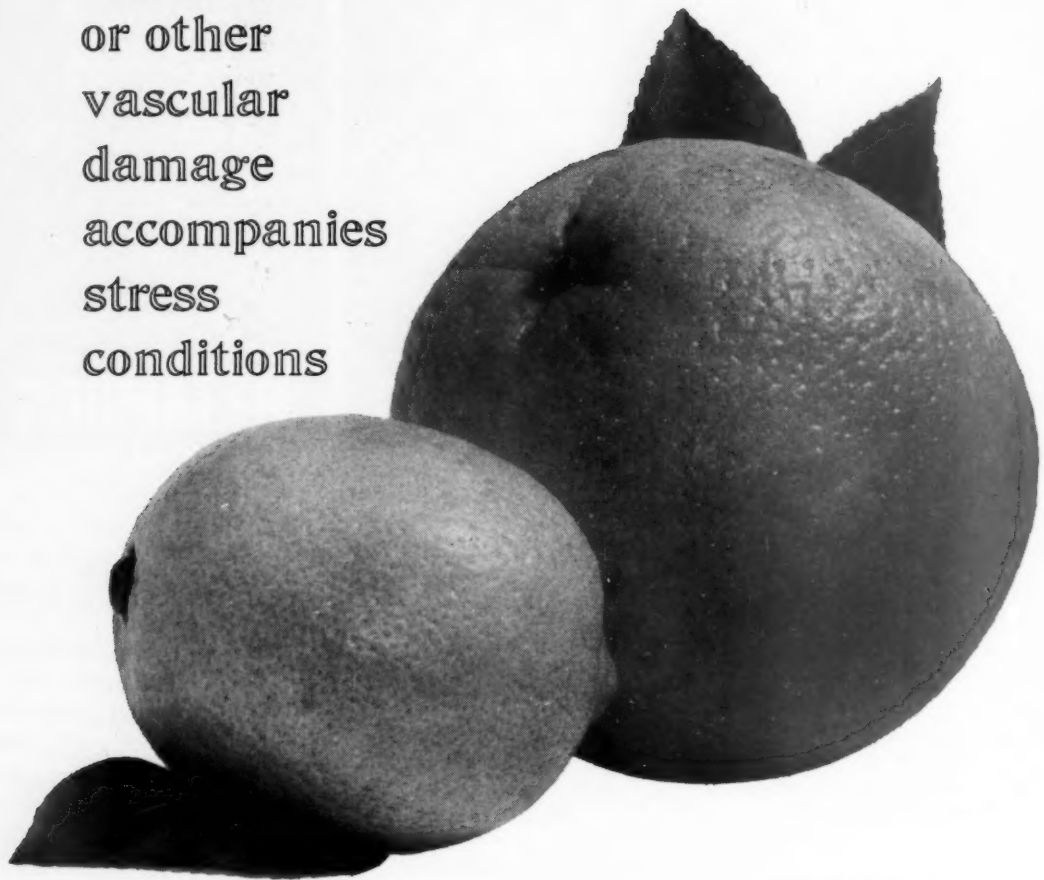
**delightful, mild  
lemon flavor**

**G. D. SEARLE & CO.**

Chicago 80, Illinois

## CITRUS BIOFLAVONOIDS

When  
capillary  
or other  
vascular  
damage  
accompanies  
stress  
conditions



*Hesperidin, Hesperidin Methyl Chalcone, or Lemon Bioflavonoid Complex* are prescribed as therapeutic adjuncts for control of vascular and capillary damage and abnormal cellular metabolism associated with many stress conditions.

These stress conditions may result from nutritional deficiencies, environment, drugs, chemicals, toxins, virus or infection.

SUNKIST AND EXCHANGE BRAND *Hesperidins* and *Lemon Bioflavonoid Complex* are available to the medical profession in specialty formulations developed by leading pharmaceutical manufacturers.

### **Sunkist Growers**

PRODUCTS SALES DEPARTMENT • PHARMACEUTICAL DIVISION  
Ontario, California



## Control of Habitual Abortion

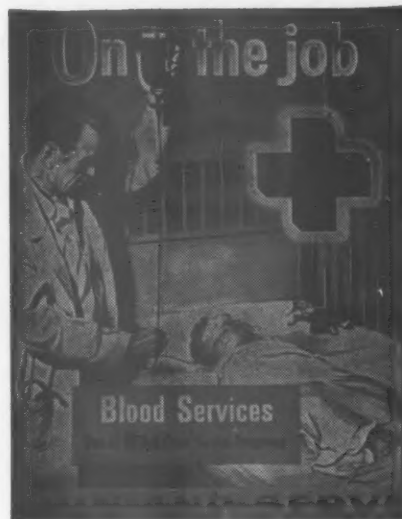
Disturbed capillary permeability and lowered capillary resistance, as well as the tendency toward edema and fluid retention, are well recognized in pregnancy (1, 2, 3, 4). The bioflavonoids have been shown effective in controlling the susceptibility to edema in pregnancy (5) and their routine prenatal use has been suggested (6).

Ecchymotic areas resulting from bruises and positive capillary fragility tests have frequently been observed in habitual aborters (7). Patients having a history of two or more spontaneous abortions have shown a marked improvement in fetal salvage after the addition of *Hesperidin* (a citrus bioflavonoid), ascorbic acid and other factors to the therapeutic regimen (8, 9, 12, 14, 15, 16). Other investigators have reported extensive use of the citrus bioflavonoids in the management of pregnancy with excellent results (18, 19, 20).

Observations include a reduction in severity or prevention of erythroblastosis fetalis in Rh-negative patients when *Hesperidin* (7) or other citrus bioflavonoids (23, 24) were administered.

The rationale of *Hesperidin* and other citrus bioflavonoids—in conjunction with vitamin C, nutritional factors or other therapeutic agents—as adjuncts in the management of pregnancy and its complications, spontaneous abortion and erythroblastosis fetalis, is based on the premise and observation that capillary involvement may be a contributing factor.

**NOTE:** For bibliography (B-688) write Sunkist Growers, Pharmaceutical Division, 720 East Sunkist Street, Ontario, California.



with your support

**RETARDED  
CHILDREN  
CAN BE  
HELPED**



**In hysterosalpingography** "Ethiodol is the drug of choice, both from a diagnostic and a therapeutic point of view"<sup>1</sup>

In a recent clinical study, the marked increase in pregnancy success rate demonstrates "the therapeutic superiority of Ethiodol hysterosalpingography over hysterosalpingography with other radiopaque media or carbon dioxide insufflation in the treatment of infertility."<sup>2</sup>

**Ethiodol** is preferred because... "It is an ideal radiopaque medium for hysterosalpingography. Because of its much lower viscosity it is preferable to... any other oily radiopaque medium. X-ray films with Ethiodol give... much better defined contrast than with any of the aqueous, acacia, or other water soluble media."<sup>2</sup>



**Ethiodol**<sup>®</sup> brand of ethiodized oil, is the ethyl ester of the iodized fatty acids of poppy seed oil, containing 37% iodine. It is available in 10 cc. ampules, boxes of two. A development of Guerbet Laboratories.

Bibliography: 1. Finegold, Wilfred J.: Internat. J. of Fertil. 3:143 1958  
2. Palmer, A.: Internat. J. of Fertil. 4:365 1959



FOUGERA

*E. Fougera & Company, Inc., Hicksville, Long Island, N. Y.*



## In premenstrual tension

### *"relieved overt symptoms"*

*In combination with a mild diuretic, "meprobamate in our series completely or virtually relieved overt symptoms of premenstrual tension in 86 of 100 women." Before therapy "... 85 per cent had temper tantrums and outbursts of fitful and inappropriate crying."\**

\*Podolsky, E.: *Journal-Lancet* 79:318 (July) 1959.

EQUANIL (meprobamate, Wyeth) relaxes mind and muscle. Hundreds of published papers attest to its efficacy in tension accompanied by anxiety, its high index of safety, its specific action, its freedom from ataxic or extrapyramidal side-effects, freedom from cumulative effects. Although rare, allergic reactions may occur; excessive dosage should be avoided in all patients. For further information on prescribing and administering EQUANIL see descriptive literature, available on request. *Wyeth Laboratories, Philadelphia 1, Pa.*

**Equanil**<sup>®</sup>  
Meprobamate,  
Wyeth





## DO YOU KNOW

- ... the exact details of how to perform the latest recommended procedures for resuscitation of the newborn?
- ... how to recognize and manage the various obstetric complications which may cause anoxia or other fetal distress?
- ... how to avoid overdosage of certain drugs which are sometimes dangerous to the fetus?

### Soon-to-be-Released

Edited by HAROLD ABRAMSON, M.D., Professor of Clinical Pediatrics, New York Medical College, New York, N. Y. Written by 24 clinicians and educators. Ready in September. Approx. 210 pages, 6 1/4" x 9 3/4", approx. 35 illustrations. About \$8.25.

### Contents

1. Anoxia and Perinatal Mortality
2. Physiology and Biochemistry
3. Pathology of the Fetus and Newborn Infant
4. Causes of Perinatal Disability in Relation to Respiratory Insufficiency
5. History and Physical Examination of the Mother
6. Obstetric Factors: Diagnosis and Management
7. Obstetric Analgesia and Anesthesia
8. Diagnosis of Fetal Distress: Clinical Signs and Electrocardiography During Labor and Delivery
9. The First Sixty Seconds of Life
10. Resuscitation Procedures in the Delivery Room
11. Mechanical Respirators and Resuscitators
12. Drug Therapy
13. Immediate Examination of the Newborn Infant in the Delivery Room
14. Recovery Nursery for Newborn Infants
15. Appraisal of Newborn Infant in the Nursery
16. Laboratory Diagnosis
17. Things to Be Done

Glossary

*Clip this Coupon  
to order on  
10-day approval!*

**Abramson**

## RESUSCITATION OF THE NEWBORN INFANT

*gives practical answers to difficult questions  
on procedures during the first few hours of life*

For the physician concerned with possible respiratory difficulties of newborn infants, this new book can serve as a very practical, down-to-earth guide to the correct procedures to follow during the first few hours of life. All of the influences at work before conception, during pregnancy, in and around the birth of the baby and immediately after birth are taken into consideration.

This new volume brings together the talents and experiences of 24 members of the Special Committee on Infant Mortality of the Medical Society of the County of New York, a panel composed of obstetricians, pediatricians, anesthesiologists and research workers. They thoroughly consider the theoretical and factual aspects of the problem in relation to practical bedside application. This is a concise volume of universal interest.

Dr. Abramson's new book discusses resuscitation not merely in terms of the use of gases and drugs and the application of physical or mechanical methods for initiation and maintenance of respiration; rather it takes a broad point of view and encompasses the investigation, early recognition and appraisal of all influences operating before conception, during pregnancy, in and around the birth of the baby and immediately after birth which may possibly contribute to neonatal respiratory insufficiency.

Particularly significant are the chapters on "History and Physical Examination of the Mother"; "Obstetric Analgesia and Anesthesia"; "Obstetric Factors: Diagnosis and Management"; and "Resuscitation Procedures in the Delivery Room."

**The C. V. MOSBY Company**

Date \_\_\_\_\_

**3207 Washington Boulevard, St. Louis 3, Missouri**

Please send me immediately upon publication a copy of RESUSCITATION OF THE NEWBORN priced at about \$8.25. I understand that if I am not completely satisfied, I can return it within 10 days without charge or obligation. I realize that if I enclose remittance with this order, I'll save the mailing charge.

☐ Payment enclosed  
(Same return privilege)

☐ Charge my account  
☐ Open a new account for me

\_\_\_\_\_  
M.D.

Address \_\_\_\_\_

City \_\_\_\_\_ Zone \_\_\_\_\_ State \_\_\_\_\_

ObGYN-7-60



in induction and stimulation of labor—method of choice

# PITOCIN

"Intravenous PITOCIN may be used successfully in elective or indicated inductions of labor. It has a definite place in the stimulation of labor in the early part or later stages either in desultory preliminary labor, or in primary or secondary uterine inertia."<sup>\*</sup>

PITOCIN (oxytocin injection, Parke-Davis) is supplied in 0.5-cc. (5-unit) ampoules, in boxes of 10 and in 1-cc. (10-unit) ampoules, in boxes of 10. Each cc. contains 10 international oxytocic units (U.S.P. units).

PARKE-DAVIS

<sup>\*</sup>Fields, H.; Greene, J. W., Jr., & Franklin, R. R.: *Obst. & Gynec.* 13:353, 1959. 33280 PARKE, DAVIS & COMPANY · Detroit 32, Michigan





the gentlest doctors in town  
stop pain with **Nupercainal**  
(dibucaine CIBA)

... For minor cuts and burns, sunburn, hemorrhoids, removing sutures, performing routine office surgery, making instrument examinations. And, to best suit every situation, there's a choice of Ointment, Cream, Lotion, Suppositories.

8/3774HB

*Complete information available on request.*

**C I B A**  
SUMMIT, N. J.

# for vaginal discharges!

# NYLMERATE

## NYLMERATE JELLY

*a proven effective agent  
in treating*

### TRICHOMONAS VAGINALIS VAGINITIS AND BACTERIAL VAGINITIS

Low surface tension allows for deep epithelial cell penetration. Kills most offending pathogens and re-establishes normal vaginal flora.

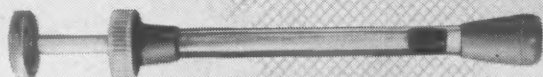
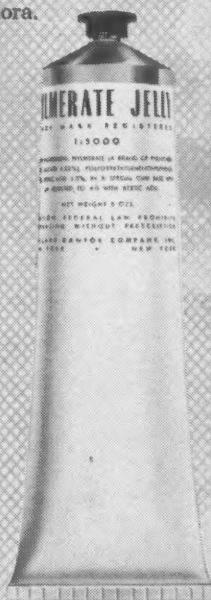
Prescribe: "Nylmerate Jelly with applicator"—5 oz. tube, also available in refill tube only. Simple to use.

Applicator—full intravaginally morning and night preceded by a Nylmerate Solution water douche. Include treatment through menstrual period.

Available only on your prescription.

#### ACTIVE INGREDIENTS

Polyoxyethylenononylphenol . . . . . 0.10%  
Phenylmercuric Acetate . . . . . 0.02%  
Boric Acid . . . . . 1.0%  
In a gum base with pH adjusted to 4



## NYLMERATE SOLUTION CONCENTRATE

*a therapeutic vaginal  
douche of choice*

Excellent adjunct in the management of monilia and trichomonas vaginal infections. Restores normal vaginal flora through a 3-prong attack. Low surface tension aids in reaching the innermost recesses where organisms flourish. Unlike vinegar, affords a controlled pH of 4.1 in dilution and is effective in any vaginal pH. Broad range activity against protozoa—bacteria—and fungi. Well suited for office use in swabbing vaginal vault.

Available only on your prescription (eliminates excessive and unwarranted douching).

Specify—Nylmerate Solution Concentrate pint bottle with measuring cap.

Prescribe two tablespoonfuls or one capful to two quarts of water twice daily.

As a prophylactic, use once a day through two menses.



#### ACTIVE INGREDIENTS

Phenylmercuric Acetate 0.2% in a buffered solvent of Alcohol 50%, Acetone 10% and de-ionized water q.s., added certified color with pH adjusted to 4.9.

Literature available



HOLLAND-RANTOS CO., INC.  
145 HUDSON STREET • NEW YORK 13, N. Y.



## in DYSMENORRHEA


"Of considerable benefit to patients whose main symptoms were headache, cramps, depression and lethargy."

J. Am. M. Women's A. 14:415 (May) 1959.

# EDRISAL®

*2 tablets every 3 hours*

Antispasmodic • Analgesic • Antidepressant



When the pain is unusually severe, prescribe  
'EDRISAL with CODEINE' ( $\frac{1}{4}$  gr. or  $\frac{1}{2}$  gr.).

**SMITH  
KLINE &  
FRENCH**





## Rapid and effective relief of pruritus vulvae... regardless of cause

HIST-A-CORT-E renders unquestionable relief of pruritus vulvae associated with either specific or non-specific affections of the female external genitalia.<sup>1</sup> HIST-A-CORT-E, a well-balanced combination of proven ingredients, not only controls inflammation, edema and pruritus . . . but facilitates healing and restores the normal tonicity and vitality of the mucosa and skin.

1. Greenblatt, R. B., Manautou, J. M., Griffin, T. L. and Henry, J. W.: *Geriatrics* 13:235-238, (April) 1958.

## HIST-A-CORT-E®

CREME (pH 4.7) LOTION

micronized hydrocortisone alcohol, vitamin A, estrone, pyrilamine maleate in the exclusive ACID MANTLE® vehicle.

DOME CHEMICALS INC.  
New York — Los Angeles — Montreal



**"For my patients who need a laxative, I recommend Caroid and Bile Salts Tablets. They relieve constipation gently and help to avoid straining. This is particularly important in cardiac and postsurgical patients."**



## **Caroid & Bile Salts** Tablets

The combined action of the principal ingredients in Caroid and Bile Salts Tablets provides 3-way, physiologic relief of constipation.

**Caroid®** — potent proteolytic enzyme for improved protein digestion.

**Bile salts** — choleric for treatment of biliary stasis; hydrotropic for soft, well-formed stools.

**Stimulaxant** — to improve smooth muscle tone, restore regularity.

**Dosage:** 1 or 2 Caroid and Bile Salts Tablets should be taken with at least 1 glass of water about 2 hours after breakfast and at bedtime.

**Samples on Request.**

American Ferment Co., Inc., 1450 Broadway, New York 18, N. Y.



Tampax gives women the freedom to swim, bathe, even skin dive, just as they would at any other time of the month.

*Millions of women have used billions of Tampax.  
Invented by a doctor for the benefit of all women  
...married or single, active or not.  
Proved by over 25 years of clinical study.*

Tampax® Internal sanitary protection is made only by Tampax Incorporated, Palmer, Mass.  
Samples and literature will be sent upon request to Dept. JOG-70

**TAMPAX**

SO MUCH A PART OF HER ACTIVE LIFE





## Before and after delivery **FLEET® ENEMA**

READY-TO-USE SQUEEZE BOTTLE



## More rapid results more comfortably

In ante- and postpartum use—Fleet Enema provides rapid, thorough action in minutes...yet patients find it much more comfortable than soapsuds.<sup>1</sup> Insertion is easy and safe because of the pre-lubricated, anatomically correct 2-inch rectal tube. Time saved with Fleet Enema permits "rapid multiparas" to be medicated earlier.<sup>1,2</sup>

Fleet Enema can be used with confidence for a variety of diagnostic and therapeutic purposes—even for patients on sodium-restricted regimens.<sup>3</sup> Systemic absorption is negligible.



100 cc. contains: 16 Gm. sodium biphosphate and 6 Gm. sodium phosphate in 4½-fl.oz. squeeze bottle.

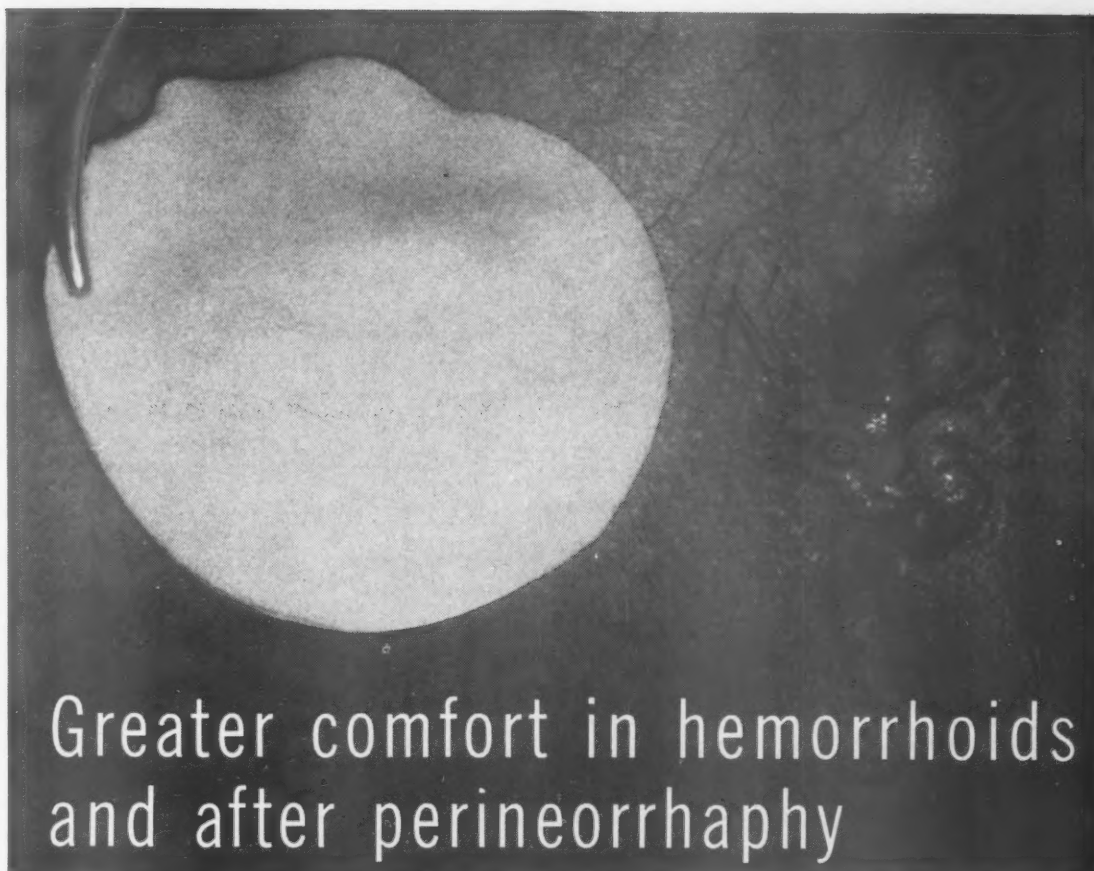
Pediatric size, 2¼ fl.oz.

Also available: Fleet Oil Retention Enema, 4¼-fl.oz. ready-to-use unit containing Mineral Oil U.S.P.

1. Rosenfield, H. H., et al.: *Obst. & Gynec.* 11:222, 1958. 2. Bookmiller, M. M., and Bowen, G. L.: *Textbook of Obstetrics and Obstetric Nursing*, ed. 3, Philadelphia, Saunders, 1958, p. 314. 3. Hellman, L. D.: *Gastroenterology*.

C. B. FLEET CO., INC. Lynchburg, Virginia





Greater comfort in hemorrhoids  
and after perineorrhaphy

when your standing orders specify...

**TUCKS®** / Soft ready-to-use cotton flannel pads  
saturated with witch hazel (50%)  
and glycerine (10%), pH about 4.6

As a dressing... *TUCKS* cools and soothes traumatized tissue... without occlusive vehicles  
or "-caine" type anesthetics.

*In the hospital, Tucks can be kept by the bedside for frequent,  
easy changing by the patient or nurse.*

As a wipe... *TUCKS* takes the trauma out of cleansing tender tissue and encourages  
more thorough hygiene.

*TUCKS* may also be sent home with patient for continuation of care.  
jars of 40 and 100.



**FULLER PHARMACEUTICAL CO.**  
3108 W. Lake Street  
Minneapolis 16, Minn.

Please send me a sample supply of TUCKS.

\_\_\_\_\_  
M. D.

Address \_\_\_\_\_

City \_\_\_\_\_ Zone \_\_\_\_\_ State \_\_\_\_\_

2

In Canada: WINLEY-MORRIS Co., Montreal

# BIOCHEMICAL PROCEDURES

**ET-3**

*a new radioactive  
in vitro test for*  
**THYROID FUNCTION**

**20**

*hours a day*

**7**

*days a week*

## Advantages:

- Patients not required to ingest radioactive material.
- Not affected by exogenous iodine administration such as X-Ray contrast media.
- Only 6 ml oxalated whole blood via air mail.

ET-3 involves the measurement of the amount of  $I^{131}$  labeled l-triiodothyronine (T-3) absorbed by the erythrocytes (E) after the addition of a measured amount of T-3 to a blood sample.

Our Isotope Division performs ET-3 studies individually, or in combination with Protein-Bound Iodine determinations (for correlation), for clients throughout North America.

Write for special Bulletin discussing technique and evaluation of ET-3.

Serving laboratories, hospitals, universities, and clinics throughout North America

## ENDOCRINE ASSAYS

Aldosterone. Catecholamines. Serotonin. 17-Ketosteroids and Beta Fraction. 17-Ketogenic Steroids. Protein-Bound Iodine. ET-3. Butanol Extractable Iodine. Estrogens, Fractionated. Pregnanediol. Pregnanetriol. Corticosteroids. Gonadotropins.

## TOXICOLOGY

Lead. Arsenic. Barbiturates. Cholinesterase. Mercury.

## SPECIALIZED DETERMINATIONS

Lipid Fractionation. Hemoglobin Identification. Protein Fractionation by Electrophoresis. Serum Iron and Iron Binding Capacity. Porphyrins. Copper. Magnesium.

Please write for Fee Schedule and Mailing Containers

"The Laboratory



for Laboratories"

**BIOCHEMICAL PROCEDURES**  
12020 CHANDLER BOULEVARD  
NORTH HOLLYWOOD, CALIFORNIA, U.S.A.



## SEND FOR YOUR COPY OF "THE BULLETIN OF LABORATORY MEDICINE"

This authoritative digest is published monthly by Biochemical Procedures to keep physicians and laboratorians abreast of current developments in the clinical laboratory field. Write for a complete set.

**orally effective progestational therapy**

# NORLUTIN<sup>®</sup>

(norethindrone, Parke-Davis)

***in conditions involving deficiency of progesterone...***

primary and secondary amenorrhea • menstrual irregularity • functional uterine bleeding • endocrine infertility • habitual abortion • threatened abortion • premenstrual tension • dysmenorrhea

**PACKAGING:** 5-mg. scored tablets, bottles of 30.

12690

**PARKE, DAVIS & COMPANY • DETROIT 32, MICHIGAN**

PARKE-DAVIS



SPORICIDAL

TUBERCULOCIDAL

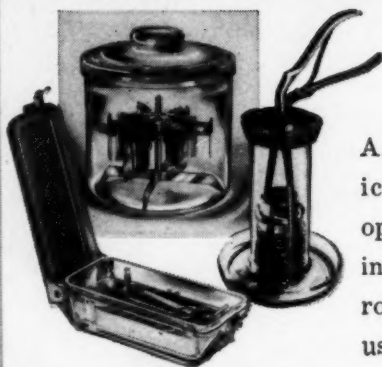
BACTERICIDAL

VIRUCIDAL

FUNGICIDAL

BARD-PARKER

# FORMALDEHYDE GERMICIDE



B-P INSTRUMENT CON-  
TAINERS—companion  
items for use with Bard-  
Parker GERMICIDE

A powerful, time-conserving chem-  
ical disinfectant for use in pre-  
operative preparation of surgical  
instruments. Non-rusting, non-cor-  
rosive, it protects and prolongs the  
useful life of surgical 'sharps.'

*Ask your dealer*



**BARD-PARKER COMPANY, INC.**  
DANBURY, CONNECTICUT

A DIVISION OF BECTON, DICKINSON AND COMPANY

B-P is a trademark



in postmenopausal vaginitis  
in vaginal plastic surgery

ORTHO®

**Dienestrol** CREAM

vaginal estrogen therapy

**builds vaginal epithelium**



# **GREATER PATIENT COMFORT** and safety with **DYCLONE**<sup>TM</sup> dyclonine hydrochloride

the unsurpassed topical anesthetic

for  
instrumentations  
examinations  
pain  
pruritus

DYCLONE does more...safely...than any  
other topical anesthetic because it is

fast-acting  
long-acting  
antibacterial  
antifungal  
nonsensitizing

supply...Dyclone Creme, tubes of 1 oz. with  
rectal applicator. Dyclone Solution, bottles  
of 1 and 8 oz.



**PITMAN-MOORE COMPANY**  
DIVISION OF ALLIED LABORATORIES, INC.  
INDIANAPOLIS 6, INDIANA



You can relieve  
cramping, heartburn,  
distention...  
as well as  
nausea and  
vomiting

**Combid<sup>®</sup>**

brand of  
prochlorperazine  
and isopropamide

b.i.d.

**Spansule<sup>®</sup>**

brand of sustained  
release capsules

'Combid' does more than simply relieve nausea and vomiting of pregnancy. Cramping, heartburn and distention—so often accompanying and complicating pregnancy—also are effectively relieved by 'Combid'.

In pregnancy, 'Combid' *Spansule* capsules reduce

- secretion
- nausea and vomiting
- spasm
- anxiety, tension and apprehension

for 10 to 12 hours after one dose.

Each 'Combid' capsule contains 10 mg. of Compazine<sup>®</sup> (brand of prochlorperazine) and 5 mg. of Darbid<sup>®</sup> (brand of isopropamide), the potent, inherently long-acting anticholinergic.

Smith Kline & French Laboratories, Philadelphia

**SMITH  
KLINE &  
FRENCH**



## Doctors, too, like "Premarin"®

**T**HE doctor's room in the hospital is used for a variety of reasons. Most any morning, you will find the internist talking with the surgeon, the resident discussing a case with the gynecologist, or the pediatrician in for a cigarette. It's sort of a club, this room, and it's a good place to get the low-down on "Premarin" therapy.

If you listen, you'll learn not only that doctors like "Premarin," but *why* they like it.

The reasons are simple. Doctors like "Premarin," in the first place, because it really relieves the

symptoms of the menopause. It doesn't just mask them — it replaces what the patient lacks — natural estrogen. Furthermore, if the patient is suffering from headache, insomnia, and arthritic-like symptoms due to estrogen deficiency, "Premarin" takes care of that, too.

"Premarin," conjugated estrogens (equine), is available as tablets and liquid, and also in combination with meprobamate or methyltestosterone.

Ayerst Laboratories • New York 16, N. Y.  
Montreal, Canada







## THE CASE OF THE FLIGHTY APPETITE...

The pickles-and-pie whims of pregnancy, real as they may be, are no laughing matter to the physician.

At a time when the need for milk nutrients is increased, and caloric restriction may be advisable, PET *Instant* Nonfat Dry Milk can play a vital role.

Here is a concentrated source of those nutrients most needed in the prenatal diet . . . and being virtually fat-free, PET *Instant* has only half the calories of whole milk. It has a delicious, sweet-fresh flavor as a beverage . . . dissolves at the touch of water. It can boost nourishment in cooking . . . added, in dry form, to dishes that ordinarily do not contain milk.

And the cost does the family budget a kindness . . . as little as 8¢ a quart.



Instantized so it dissolves almost at the touch of water.

All the protein, calcium and B-vitamins of whole milk without the fat



©1959

—PET MILK COMPANY • ST. LOUIS 1, MISSOURI—

*the decorative jar makes a therapeutic difference*

The FILIBON jar is a handsome and handy reminder for everyday prenatal nutritional support. You can be sure she will be reminded of her FILIBON-a-day... and that the up-to-the-minute formula covers nutritional defenses throughout pregnancy.

FILIBON provides ferrous fumarate, an iron well-tolerated by even the most easily upset patients. Each small, dry-filled capsule also includes vitamin K and AUTRINIC® Intrinsic Factor Concentrate that enhances, never inhibits, B<sub>12</sub> absorption. For complete formula see Physicians' Desk Reference, page 688.

LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, N. Y.



Phosphorus-free FILIBON® Prenatal Capsules Lederle



# THE "PHYSICIAN'S METHOD" COMPLETE....FOR CONTRACEPTION

The more satisfied patient will be motivated to follow your instructions for regular use. Recommend the KOROMEX COMPACT to your patients . . . make it possible for them to determine whether Jelly or Cream is best suited to their individual requirements.

## EACH KOROMEX COMPACT contains:

Koromex Jelly—regular size tube  
Koromex Cream—trial size  
Koromex Diaphragm—Coil Spring  
Koromex Introducer



*(Koromex cream and sanitary zippered plastic clutch bag supplied at no extra charge)  
Always insist on the use of time-tested Koromex Jelly or Cream with a diaphragm.*



HOLLAND-RANTOS CO., INC.

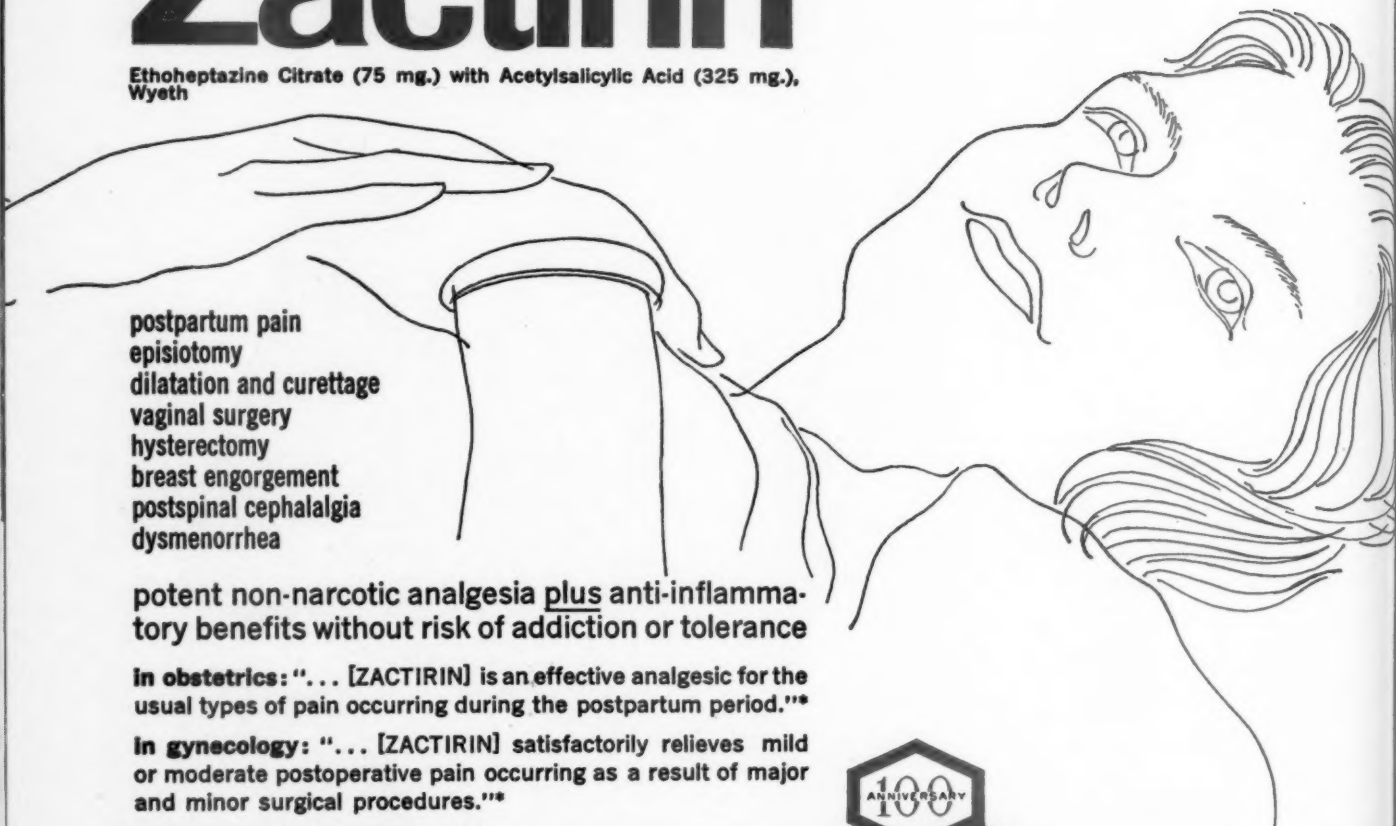
145 HUDSON STREET • NEW YORK 13, N. Y.

# ob- gyn

pain relief

## Zactirin®

Ethoheptazine Citrate (75 mg.) with Acetylsalicylic Acid (325 mg.),  
Wyeth



postpartum pain  
episiotomy  
dilatation and curettage  
vaginal surgery  
hysterectomy  
breast engorgement  
postspinal cephalalgia  
dysmenorrhea

potent non-narcotic analgesia plus anti-inflammatory  
benefits without risk of addiction or tolerance

**In obstetrics:** "... [ZACTIRIN] is an effective analgesic for the  
usual types of pain occurring during the postpartum period."<sup>\*</sup>

**In gynecology:** "... [ZACTIRIN] satisfactorily relieves mild  
or moderate postoperative pain occurring as a result of major  
and minor surgical procedures."<sup>\*\*</sup>

**Supplied:** Tablets, bottles of 48.

<sup>\*</sup>Roden, J.S., and Haugen, H.M.: Evaluation of a New Analgesic Com-  
bination, Missouri Med. 55:128 (Feb.) 1958.

For further information on prescribing and administering ZACTIRIN  
see descriptive literature, available on request.

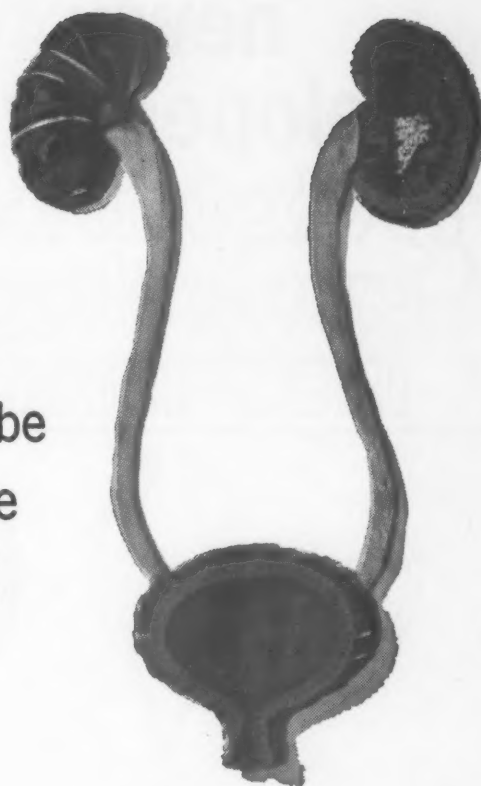
Wyeth Laboratories Philadelphia 1, Pa.



A Century of Service to Medicine



Just a "simple"  
case of cystitis  
may be the  
precursor of  
pyelonephritis<sup>1</sup>—  
or may actually be  
the first evidence  
of a pre-existing  
pyelonephritic  
process.<sup>2</sup>



WHEN TREATING CYSTITIS—SPECIFY

**FURADANTIN<sup>®</sup>**

brand of nitrofurantoin

to ensure rapid control of infection  
throughout the urogenital system

FIRST

Rapid bactericidal action against a wide range of gram-positive and gram-negative bacteria including organisms such as staphylococci, Proteus and certain strains of Pseudomonas, resistant to other agents

- actively excreted by the tubule cells in addition to glomerular filtration
- negligible development of bacterial resistance after 8 years of extensive clinical use
- excellent tolerance—nontoxic to kidneys, liver and blood-forming organs
- safe for long-term administration

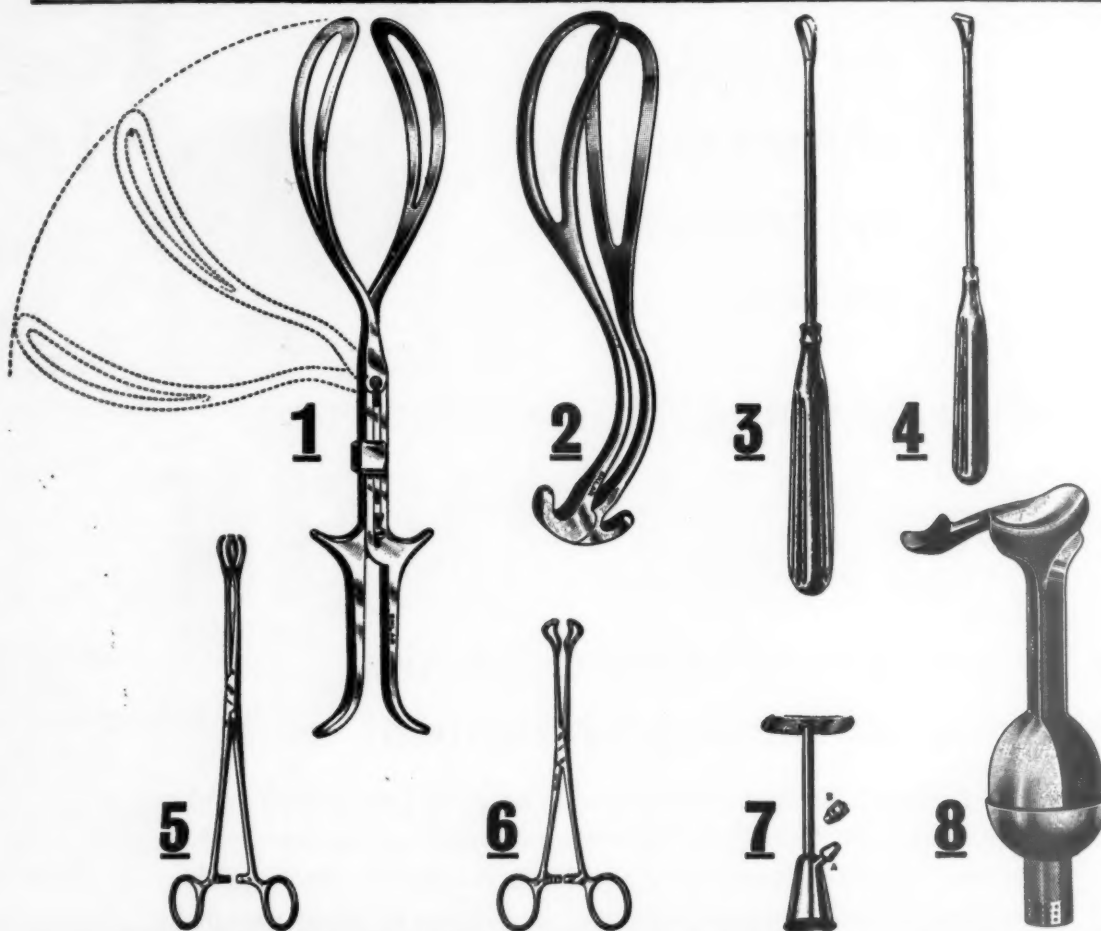
AVERAGE FURADANTIN ADULT DOSAGE: 100 mg. q.i.d. with meals and with food or milk on retiring. Supplied: Tablets, 50 and 100 mg.; Oral Suspension, 25 mg. per 5 cc. tsp.

REFERENCES: 1. Campbell, M. F.: Principles of Urology, Philadelphia, W. B. Saunders Co., 1957. 2. Colby, F. H.: Essential Urology, Baltimore, The Williams & Wilkins Co., 1953.

NITROFURANS—a unique class of antimicrobials—neither antibiotics nor sulfonamides

EATON LABORATORIES, NORWICH, NEW YORK

# newly developed by **SKLAR** & obstetrical & gynecological instruments



1. Laufe-Barton-Kieland Obstetrical Forceps / with hinged blade combining the advantages of the Barton and Kieland models in management of transverse and posterior positions of fetal head.
2. Laufe-Piper Obstetrical Forceps / with classical Piper blades, new short shanks and accentuated perineal curve.
3. Lounsbury Placenta Curette / with extra long malleable shaft and large sharp blade 22mm. wide.
4. Holtz Endometrial Curette / designed to insure recovery of tissue from any part of the uterine cavity.
5. Gutglass Cervix Hemostatic Forceps / provides more effective hemostasis for cervical lacerations by permitting the sutures to be placed inside ring of jaws.
6. Bunim Urethral Clamp / facilitates fixation of the urethra to the periostium of the retropubis in Marshall-Marchetti procedure.
7. Perell Fetoscope / for auscultation of fetal heart tones. Available in Luer-Lok and slip-on models; may be used with any Bowles Type Stethoscope.
8. Mason Auvard Vaginal Speculum / with specimen cup; extra long concave blade prevents slipping from vagina.



## enhanced obstetrical analgesia

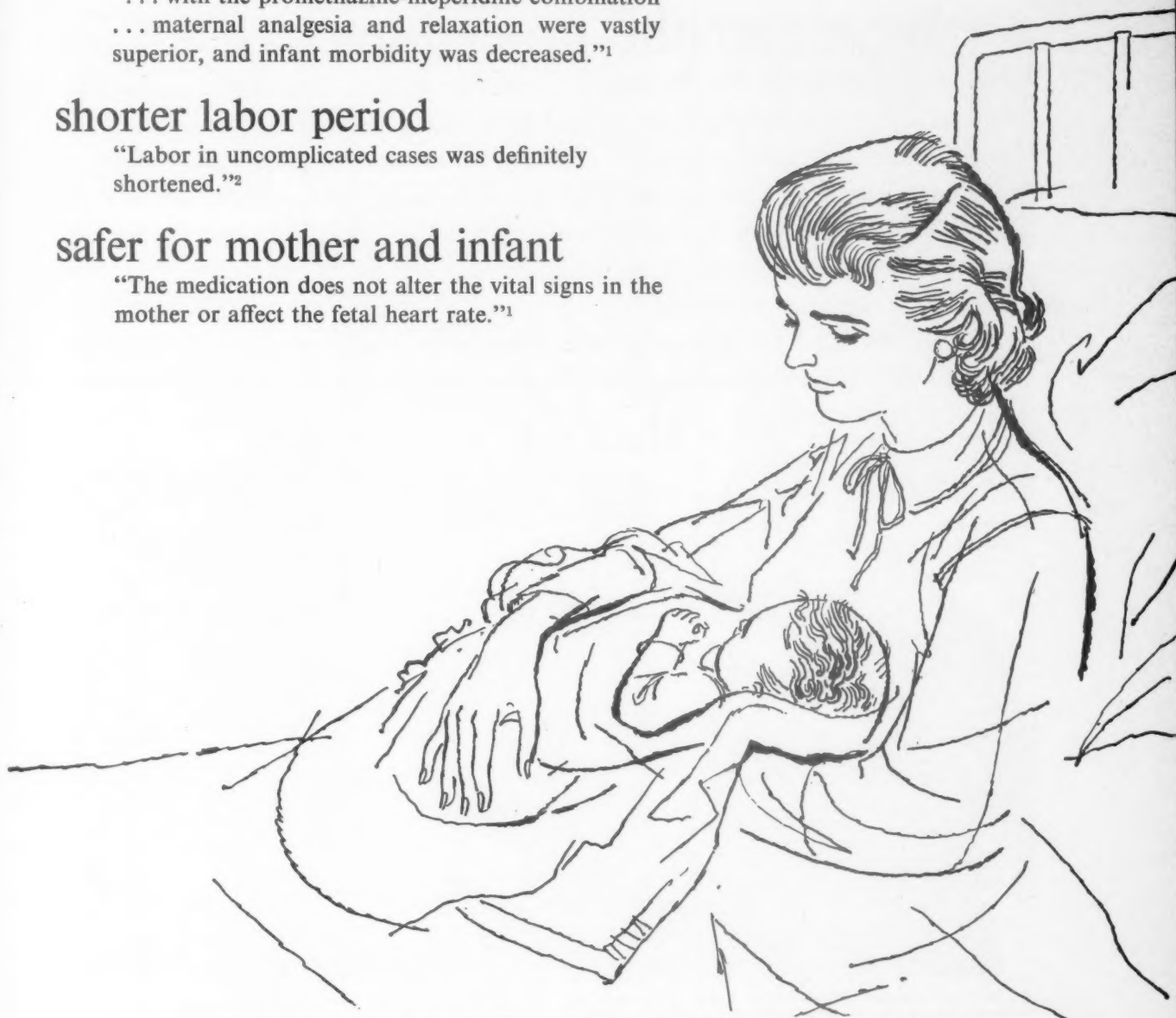
"... with the promethazine-meperidine combination  
... maternal analgesia and relaxation were vastly  
superior, and infant morbidity was decreased."<sup>1</sup>

## shorter labor period

"Labor in uncomplicated cases was definitely  
shortened."<sup>2</sup>

## safer for mother and infant

"The medication does not alter the vital signs in the  
mother or affect the fetal heart rate."<sup>1</sup>



analgesic, amnesic, antiemetic and antihistaminic actions

meperidine-promethazine combined

# MEPERGAN<sup>®</sup>

Promethazine Hydrochloride and Meperidine Hydrochloride, Wyeth

For further information on prescribing and administering MEPERGAN see descriptive literature, available on request.

1. Carroll, J.J., and Moir, R.S.: J.A.M.A. 168:2218-24 (Dec. 27) 1958. 2. Gordon, L.E., and Ruffin, C.L.: Am. J. Obst. & Gynec. 76:147-151 (July) 1958.

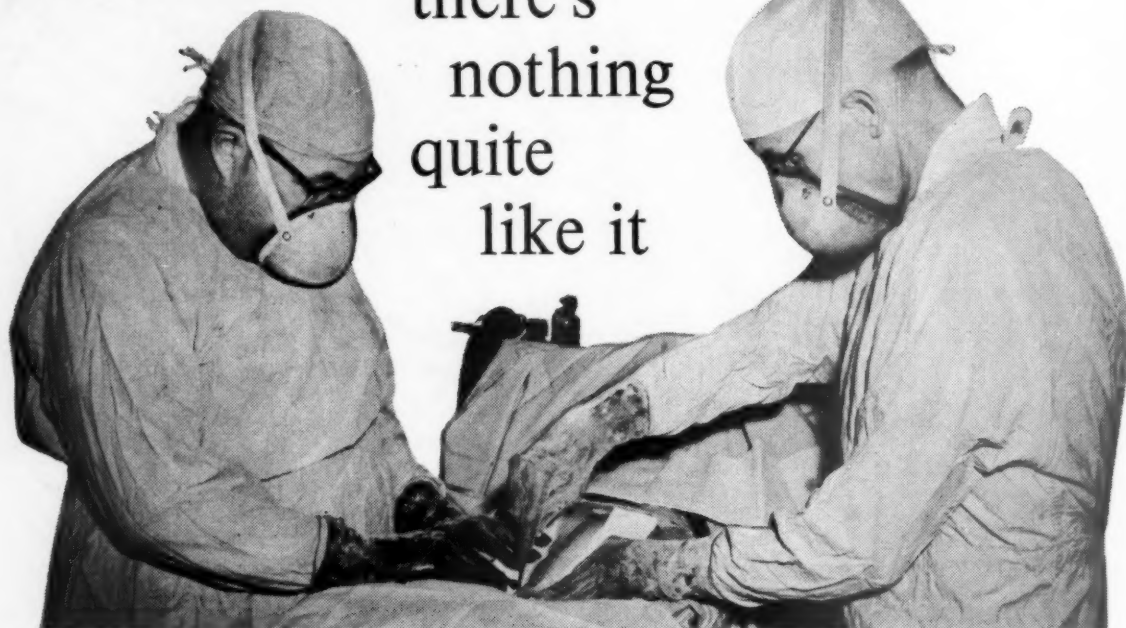
Wyeth Laboratories Philadelphia 1, Pa.



A Century of  
Service to Medicine

**Whatever the procedure** a truly sterile operative field can be maintained by this new skin isolation technic. Regardless of anatomic location, contour, or intricacy—Vi-Drape® Film isolates the wound from the patient's own skin bacteria. Vi-Drape Film is a soft, pliant transparent plastic sheet which is adhered intimately and firmly to the surgically prepared skin of the operative field with Vi-Hesive® Adherent. Incision is then made right through the plastic bacterial barrier so that protection is complete to the incisional edge. It will not come loose to permit accidental contamination even during lengthy, complicated procedures. Vi-Drape Film eliminates the need for interfering skin towels and clips, and thus affords clear visibility of the entire operating field as well as easier approach. It is impermeable to bacteria and fluids.

there's  
nothing  
quite  
like it



**Incise right through the Vi-Drape Film.** Wider field of visibility facilitates identification of landmarks. Extensive sterile field is maintained for second incisions or double approach. For example—in bilateral herniorrhaphy incisions, the large linen drape can be shifted without fear of contamination. In inguinal hernia and orchidopexy, the scrotum remains visible and accessible

for palpation, and at the same time is completely sealed out of the operative field. In aortal femoral bypass procedures, Vi-Drape Film applied extensively can achieve a degree of asepsis previously considered impossible, since it allows access to a sterile abdominal field as well as in both femoral canals simultaneously, without danger of contamination from the perineal area.



**At closure suturing is completed to skin level,** then the transparent film is peeled back from wound edges, and skin suturing completed before the entire film is peeled off. Some surgeons prefer to suture right through the film, leaving a small piece intact under the sutures. Following either method, Aeroplast® Surgical Dressing can be sprayed on as the definitive dressing. It forms a tough but flexible plastic film dressing impermeable to environmental contamination and requiring infrequent changes. Photos at left and above courtesy Ralph Adams, M. D., Boston, Mass. and Wolfeboro, N. H.



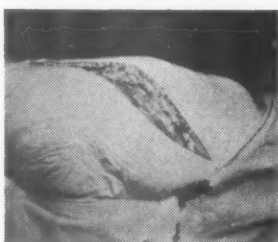


**Basic technic** When freshly "prepped" skin is dry, Vi-Hesive Adherent is sprayed on to an even pink tint from about 12" distance. Sterilized Vi-Drape Film is held taut over proposed operative area then smoothly molded by hand to site and wide adjacent skin area. Photo courtesy Ralph Adams, M.D.

**Sealing off the contaminated colostomy or ileostomy, and yet having it visible while exploring a new operative field, is made possible by the application of Vi-Drape Film to the entire area.** Photo courtesy of Robert M. Zollinger, M.D., William G. Pace, M.D. and Marjorie J. Reed, R.N., Columbus, Ohio.

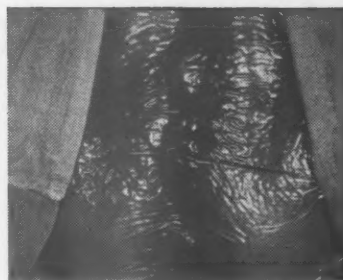
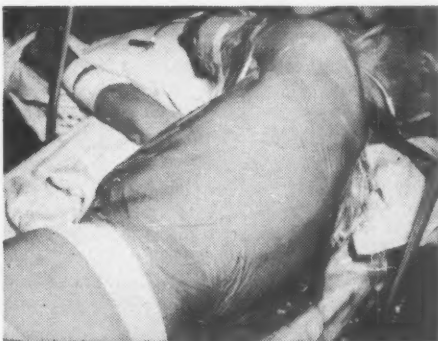


**Visibility of landmarks, maintenance of asepsis in operative areas previously hard-to-drape, and isolation of the entire operative zone are particular surgical advantages of using Vi-Drape Film in neurosurgery.** Illustrative is the isolation of the cervical occipital area for laminectomy shown above. Photo courtesy Arthur B. Eisenbrey, M.D., Detroit, Mich.



**Smooth molding and close adherence of the plastic film to the difficult contour of the hip, provides an aseptic operative area previously considered almost impossible to achieve.** Vi-Drape Film clings closely to the skin throughout long procedures. Photo courtesy Chas. G. Lovingood, M.D., Frank L. Shively, Jr., M.D. and Albert M. Storrs, M.D., Dayton, Ohio.

**Large areas can be sealed off for thoracic or cardiovascular surgery without hiding landmarks.** Neck and shoulders are completely isolated from the incision. A cleaner, drier operative field is possible using Vi-Drape Film. When Aeroplast Surgical Dressing is used postoperatively, evaluation of healing can be made without removing dressings. Photo courtesy Curtis P. Artz, M.D., Jackson, Miss.



**Isolation of the anal area from the vaginal orifice during correction of prolapse of the vaginal vault avoids contamination by fecal extrusions.**

**Exteriorized vaginal vault is protected from contamination by Vi-Drape Film clinging closely to vaginal orifice during procedure and by isolation of the anus.** Photos courtesy C. Paul Hodgkinson, M.D., Detroit, Mich.



**To prevent trauma, desiccation and infection — Vi-Drape Film is frequently used as a protective wrap for exposed organs as shown above holding intestines during an aortic graft.** Photo courtesy Chas. G. Lovingood, M.D., Frank L. Shively, Jr., M.D. and Albert M. Storrs, M.D., Dayton, Ohio

**Would you like to see a full-color sound motion picture further illustrating the application of Vi-Drape Film in varied surgical procedures? The film, "A New Transparent Plastic Surgical Drape," produced by Robert M. Zollinger, M.D., William G. Pace, M.D. and Marjorie J. Reed, R.N., at Ohio State University Department of Surgery, is available for showing to all members of the surgical team.**

**Please send requests to:**  
**AEROPLAST CORPORATION**  
Station A—Box 1, Dayton 3, Ohio

Vi-Drape® Film, Vi-Hesive® Adherent—Pats. Pend.  
Aeroplast® Dressing—U.S. Pat. No. 2,804,073  
All photos shown are of actual procedures.



**DREAMS NEED SOME HELP.** Saving with U.S. Savings Bonds is a good way to turn a dream into reality. The Payroll Savings Plan makes saving automatic.

## Let the Government Pay You for saving for something you want

An installment plan that pays you interest sounds surprising, doesn't it? That's what happens when you buy U.S. Savings Bonds. They now pay you  $3\frac{3}{4}\%$  compounded semi-annually when held to maturity. With this new rate, \$3 becomes \$4 fourteen months faster than before—in just 7 years, 9 months. Make your dreams come true, faster than ever, with U.S. Savings Bonds.

### ADVANTAGES WORTH THINKING ABOUT

- You can save automatically with the Payroll Savings Plan • You now earn  $3\frac{3}{4}\%$  interest to maturity • You invest without risk under a U.S. Government guarantee • Your money can't be lost or stolen • You can get your money, with interest, anytime you want it • You save more than money—you help your Government pay for peace • Buy Bonds where you work or bank.

*NOW every Savings Bond you own—old  
or new—earns  $\frac{1}{2}\%$  more than ever before.*

You save more than money with U.S. Savings Bonds

*The U.S. Government does not pay for this advertising.  
The Treasury Department thanks The Advertising Council  
and this magazine for their patriotic donation.*





# The Pregnant

- and a natural way to meet her special need for calcium  
- with low-calorie **Carnation Instant**

Drinking enough milk during pregnancy to assure sufficient calcium has posed the problem of unwanted fat calories — till recently.

Now a *natural* way to help assure your patients' good calcium and nutritional status is the excellent new food — *new Carnation Instant Nonfat Dry Milk mixed 25% over-strength.*

One-third cup extra crystals per liquid quart when mixing provides 25% more cal-

cium, protein, and B-vitamins than ordinary nonfat milk. Because your patients can add this additional amount of Carnation Instant Nonfat, they get *needed* nutrition — *without* excessive calories. Its richer, more delicious flavor is a *natural* way to *extra* nutrition they will enjoy. Costs them only 10¢ a quart.



ANOTHER QUALITY PRODUCT OF CARNATION COMPANY, LOS ANGELES 36, CALIFORNIA



*Only the new edition of this popular guide  
can keep you abreast of recent advances*

**Learn how to identify such  
newly recognized diseases as:**

Pulmonary alveolar proteinosis  
Cat-scratch disease  
Familial chronic idiopathic jaundice  
Kwashiorkor  
Epidemic hemorrhagic fever  
Thrombotic thrombocytopenic purpura  
Aldosteronism  
Carcinoid syndrome

**Learn importance of new cellular  
discoveries in such areas as:**

Sex chromatin  
LE cell  
Mast cells

**Study new information on  
these and other diseases:**

Histoplasmosis  
Toxoplasmosis  
Hemoglobinuric nephrosis  
Renal papillary necrosis  
Vacuolar nephropathy of potassium  
deficiency  
Uremic pneumonitis  
Hyaline disease of the lung  
Atypical hyperplasias in the lung  
Viral hepatitis  
Postnecrotic cirrhosis of the liver  
Fibrocystic disease of the pancreas  
Varying effects of pancreatic islet cell  
tumors  
Hashimoto's thyroiditis  
Relationship of giant cell pneumonia  
and measles  
Amniotic fluid embolism  
Fibrous dysplasia of bone  
Eosinophilic granuloma of bone

**Review the changing concepts  
of these vascular diseases:**

Endarterial thrombi in the pathogenesis  
of atheroma  
Intimal vascularization and hemorrhage  
in atherosclerosis

**Gain new understandings of these  
diseases resulting from improved  
cytologic diagnosis:**

Hemangiopericytoma  
Alveolar soft part sarcoma  
Mesenchymoma  
Keratoacanthoma  
Juvenile melanoma

*Just Published! New 5th Edition Anderson*

## **SYNOPSIS OF PATHOLOGY**

As the only frequently revised, concise and yet complete and authoritative pathology guidebook available, **SYNOPSIS OF PATHOLOGY**, just released in a new 5th edition, is the only book that can keep you fully informed on all of the current developments in all areas of general and special pathology.

For this new edition, the book has been thoroughly revised to reflect the increase or decrease in incidence of some diseases, discoveries of new pathological entities, changes in the fundamental nature or our understanding of certain diseases and many other advances and discoveries in such specific areas as are listed in the column on the left.

This popular book is a classic in its own right. Never has one man presented so much information on all areas of pathology in so little space. It is so complete, so concisely presented and so well illustrated, that it has a universal appeal shared by few other publications in pathology.

You will find that the first few chapters cover basic principles of pathology. For example, you'll review how inflammation, repair, and regeneration take place; you'll understand more about retrograde changes which are disturbances of metabolism as demonstrated by atrophy and injury by ionizing irradiation; and you'll read about the latest ideas on disturbances of circulation.

Later, bacterial infection is thoroughly discussed and all of the effects on the body of pathologic bacteria are fully brought out. Specific organisms, such as streptococcus and staphylococcal infections are thoroughly discussed and their important relationship to wound infection is clarified. Spirochetal and venereal diseases, mycotic and protozoal and helminthic infections and infestations are thoroughly described. Chemical poisons, nutritional disturbances, vitaminoses and disturbances of growth are also covered in this broad first section of the book on general pathology.

The remaining 13 chapters of the book give you a well illustrated outline, with sufficient detail, of all of the diseases affecting the various systems of the body—cardio-vascular, gastrointestinal, respiratory, endocrine, reticulo-endothelial, etc.—all expressing the most current facts and accepted opinions in each area.


By **W. A. D. ANDERSON, M.A., M.D., F.A.C.P., F.C.A.P.**, Professor of Pathology, University of Miami School of Medicine; Director of Pathology Laboratories, Jackson Memorial Hospital, Miami, Florida. Just published. 5th edition, 876 pages, 4 1/8" x 7 5/8", 414 text illustrations, 4 color plates. Price, \$9.25.

*Order Any of Three Ways:*

*At Your Favorite Bookstore;  
From Your Professional Sales Representative;  
Or Direct on 10 Day Approval From*

**The C. V. MOSBY Company**  
3207 Washington Boulevard, St. Louis 3, Missouri





Thanks to your prompt treatment and the smooth action of Deprol, your patient's depression is relieved and her anxiety calmed—often in two or three days. She eats properly, sleeps well, and her depression no longer complicates your basic regimen.

## Lifts depression...as it calms anxiety!

**For pregnant, postpartum and menopausal patients —  
a smooth, balanced action that lifts depression  
as it calms anxiety...rapidly and safely**

**Balances the mood—no “seesaw” effect of amphetamine-barbiturates and energizers.** While amphetamines and energizers may stimulate the patient—they often aggravate anxiety and tension. And although amphetamine-barbiturate combinations may counteract excessive stimulation—they often deepen depression.

In contrast to such “seesaw” effects, Deprol lifts depression as it calms anxiety.

**Acts swiftly—the patient often feels better, sleeps better, within two or three days.** Unlike most other antidepressant drugs, Deprol relieves the patient quickly—often within two or three days.

**Acts safely—no psychotic reactions.** Deprol does not cause hypotension, tachycardia, jitteriness, or liver toxicity. It can be safely administered with basic therapy.

**Dosage:** Usual starting dose is 1 tablet q.i.d. When necessary, this may be gradually increased up to 3 tablets q.i.d.  
**Composition:** 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.  
**Supplied:** Bottles of 50 light-pink, scored tablets. Write for literature and samples.

# Deprol<sup>®</sup>

 **WALLACE LABORATORIES**  
New Brunswick, N. J.

621-758



## WHITE COTTON GOWNS 48" Long—O.K. for X-Ray

#2G—Crinkle Cloth requires NO IRONING

#3G—Shrunk Cotton Sheeting.

COLOR of TIES tells SIZE  
2 is best size

-----Size 1 small (blue ties)—42"  
-----Size 2 medium (white ties)—52"  
-----Size 3 large (pink ties)—60"

Actual  
bust of  
gowns

Pay with order and we pay postage.

TECKLA, Box 863, Worcester, Mass. Phone PL 2-5236

Send: Crinkle or Plain

6 for \$14.00 12 for \$26.00 24 for \$51.00

SIZE 1. 2. 3. BACK OPEN 12" 24" 48"

On Duty in 50 States.

"100% Cotton"

TECKLA

## Changing Your Address?

### WHEN YOU MOVE, PLEASE—

- (1) Notify us to change your address—allow us six weeks to make the change.
- (2) Mention the name of this Journal. (We publish twelve periodicals.)
- (3) Give us your old address. If possible, return the addressed portion of the envelope in which we sent your last copy.
- (4) Give us your new address—complete—including the Postal zone number.
- (5) Please print your name and address.

### Thank You!

Circulation Department, The C. V. Mosby Company, Publishers, 3207 Washington Blvd., St. Louis 3, Mo.



## Preserve Your Journals With This *Jesse Jones* Volume File

Specially designed and produced for *American Journal of Obstetrics and Gynecology*, this file will keep one volume, or six issues, clean, orderly and readily accessible. Picture this distinctive, sturdy Volume File on your bookshelf. Its rich red and green Kivar cover looks and feels like leather, and the 16-karat gold leaf hot-embossed lettering makes it a fit companion for your finest bindings. The Volume File is reasonably

priced, in spite of its costly appearance. It is sent postpaid, carefully packed, for \$2.50 each. Most subscribers will find it more convenient and economical to order 3 for \$7.00 or 6 for \$13.00. When ordering specify file for *American Journal of Obstetrics and Gynecology*. Send check with order. *Satisfaction guaranteed.* Can be sent to U.S. and possessions only. For prompt shipment, order direct from

*Jesse Jones Box Corporation*

P.O. BOX 5120, PHILADELPHIA 22, PENN.

(Since 1843)



A  
GUIDE  
TO

# THE REALMS OF THERAPY BEST ATTAINED WITH



# ATARAX®

(brand of hydroxyzine)

World-wide record of effectiveness—over 200 laboratory and clinical papers from 14 countries.  
Widest latitude of safety and flexibility—no serious adverse clinical reaction ever documented.  
Chemically distinct among tranquilizers—not a phenothiazine or a meprobamate.  
Added frontiers of usefulness—antihistaminic; mildly antiarrhythmic; does not stimulate gastric secretion.

## Special Advantages



unusually safe; tasty syrup,  
10 mg. tablet



well tolerated by debilitated  
patients



useful adjunctive therapy for  
asthma and dermatosis; particularly effective in urticaria



does not impair mental acuity

## Supportive Clinical Observation

"... Atarax appeared to reduce anxiety and restlessness, improve sleep patterns and make the child more amenable to the development of new patterns of behavior..." Freedman, A. M.: *Pediat. Clin. North America* 5:573 (Aug.) 1958.

"... seems to be the agent of choice in patients suffering from removal disorientation, confusion, conversion hysteria and other psychoneurotic conditions occurring in old age." Smigel, J. O., et al.: *J. Am. Geriatrics Soc.* 7:61 (Jan.) 1959.

"All [asthmatic] patients reported greater calmness and were able to rest and sleep better... and led a more normal life... In chronic and acute urticaria, however, hydroxyzine was effective as the sole medication." Santos, I. M., and Unger, L.: Presented at 14th Annual Congress, American College of Allergists, Atlantic City, New Jersey, April 23-25, 1958.

"... especially well-suited for ambulatory neurotics who must work, drive a car, or operate machinery." Ayd, F. J., Jr.: *New York J. Med.* 57:1742 (May 15) 1957.

## ...and for additional evidence

Bayart, J.: *Acta paediat. belg.* 10:164, 1956. Ayd, F. J., Jr.: *California Med.* 87:75 (Aug.) 1957. Nathan, L. A., and Andelman, M. B.: *Illinois M. J.* 112:171 (Oct.) 1957.

Settel, E.: *Am. Pract. & Digest Treat.* 8:1584 (Oct.) 1957. Negri, F.: *Minerva med.* 48:607 (Feb. 21) 1957. Shalowitz, M.: *Geriatrics* 11:312 (July) 1956.

Eisenberg, B. C.: *J.A.M.A.* 169:14 (Jan. 3) 1959. Coirault, R., et al.: *Presse méd.* 64:2239 (Dec. 26) 1956. Robinson, H. M., Jr., et al.: *South. M. J.* 50:1282 (Oct.) 1957.

Garber, R. C., Jr.: *J. Florida M. A.* 45:549 (Nov.) 1958. Menger, H. C.: *New York J. Med.* 58:1684 (May 15) 1958. Farah, L.: *Internat. Rec. Med.* 169:379 (June) 1956.

**SUPPLIED:** Tablets, 10 mg., 25 mg., 100 mg.; bottles of 100. Syrup (10 mg. per tsp.), pint bottles. Parenteral Solution: 25 mg./cc. in 10 cc. multiple-dose vials; 50 mg./cc. in 2 cc. ampoules.



New York 17, N. Y.  
Division, Chas. Pfizer & Co., Inc.  
Science for the World's Well-Being

**New!...**  
**for**  
**appetite**  
**control**



## **Controls compulsive overeating**

**CURBS APPETITE...RELIEVES TENSION HUNGER...  
TRANQUILIZES "DIET JITTERS"**

Why do so many overweight patients so often break their diets?

The reason is usually tension.<sup>1,2,3</sup> Now—Appetrol has been formulated to help you solve this problem.

Appetrol provides dextro-amphetamine to curb your patient's appetite. Even more important, it provides meprobamate to control compulsive overeating, to ease the frustration of the dietary regimen—and to minimize the jittery effects of amphetamine.

**Usual dosage:** 1 or 2 tablets one-half to 1 hour before meals. Each tablet contains: 5 mg. dextro-amphetamine sulfate and 400 mg. meprobamate.

**Available:** Bottles of 50 pink, scored tablets.

Thus, Appetrol does more than other anorectics which merely suppress appetite. Appetrol also tranquilizes tension hunger to give more complete control of compulsive overeating. Your patients find it easier to stay on their diets—even during prolonged periods.

**References:** 1. Freed, S. C.: Psychic factors in the development and treatment of obesity. *J.A.M.A.* 133:369, Feb. 8, 1947. 2. Kotkov, B.: Group psychotherapy with the obese. Paper read before The Academy of Psychosomatic Medicine, Oct. 1958. 3. Plotz, M.: Modern management of obesity—the "social diet." *J.A.M.A.* 170:1513, July 25, 1959.

# **Appetrol®**

DEXTRO-AMPHETAMINE + MEPROBAMATE


**for appetite control**



**WALLACE LABORATORIES / New Brunswick, N. J.**



direct  
uterine  
relaxation  
without  
hormonal action

a myo--vascular relaxant

**VASODILAN<sup>®</sup>**  
Pronounced VĀ-ZŌ-DY-LAN Isoxsuprine hydrochloride, Mead Johnson<sup>1,2</sup>  
relieves painful menstrual cramps

*dosage*—For painful menstrual cramps, give 10 or 20 mg. (1 or 2 tablets) three or four times daily 24 to 72 hours prior to the expected onset of menstruation.

*references:* (1) Voulgaris, D. M.: Dysmenorrhea—Treatment with Isoxsuprine, *Obstetrics and Gynecology*, to be published. (2) Busky, A. H., to be published. 88768



Mead Johnson  
Symbol of service in medicine

EVANSVILLE 21, INDIANA

**CONSISTENTLY GOOD  
CLINICAL RESULTS  
IN TRICHOMONAL  
AND MONILIAL VAGINITIS**

**TRICOFURON IMPROVED** (Suppositories and Powder)  
cured 143 of 161 patients with vaginitis due to  
*Trichomonas vaginalis*, *Candida* (*Monilia*) *albicans*,  
or both. "Almost immediate symptomatic  
improvement was noted with the first insufflation."

Criteria for cure: freedom from  
infecting organisms as well as symptoms on  
repeated examinations during a three-month follow-up.  
This cure rate of 88.8% is "surprisingly similar"  
to results reported by earlier investigators.

Coolidge, C. W.; Glisson, C. S., and Smith, A. S.:  
*J.M.A. Georgia* 48:167, 1959.

**TRICOFURON®  
IMPROVED**

**2-step treatment brings swift relief,  
eradicates stubborn trichomonads,  
*Candida* (*Monilia*) *albicans*,  
*Hemophilus vaginalis***

**1. POWDER** for weekly insufflation in your office.

**MICOFUR®**, brand of nifuroxime, 0.5%  
and **FUROXONE®**, brand of furazolidone, 0.1% in  
an acidic water-dispersible base.

**2. SUPPOSITORIES** for continued home use

—1st week one suppository in the morning  
and one on retiring. After 1st week, one  
suppository at night may suffice.

Continue use of suppositories during menses.  
Treatment should be continued throughout a complete  
menstrual cycle and for several days thereafter.

**MICOFUR** 0.375% and **FUROXONE** 0.25%  
in a water-miscible base.

*Rx new box of 24 suppositories with applicator  
for more practical and economical therapy.*

*Also available:*

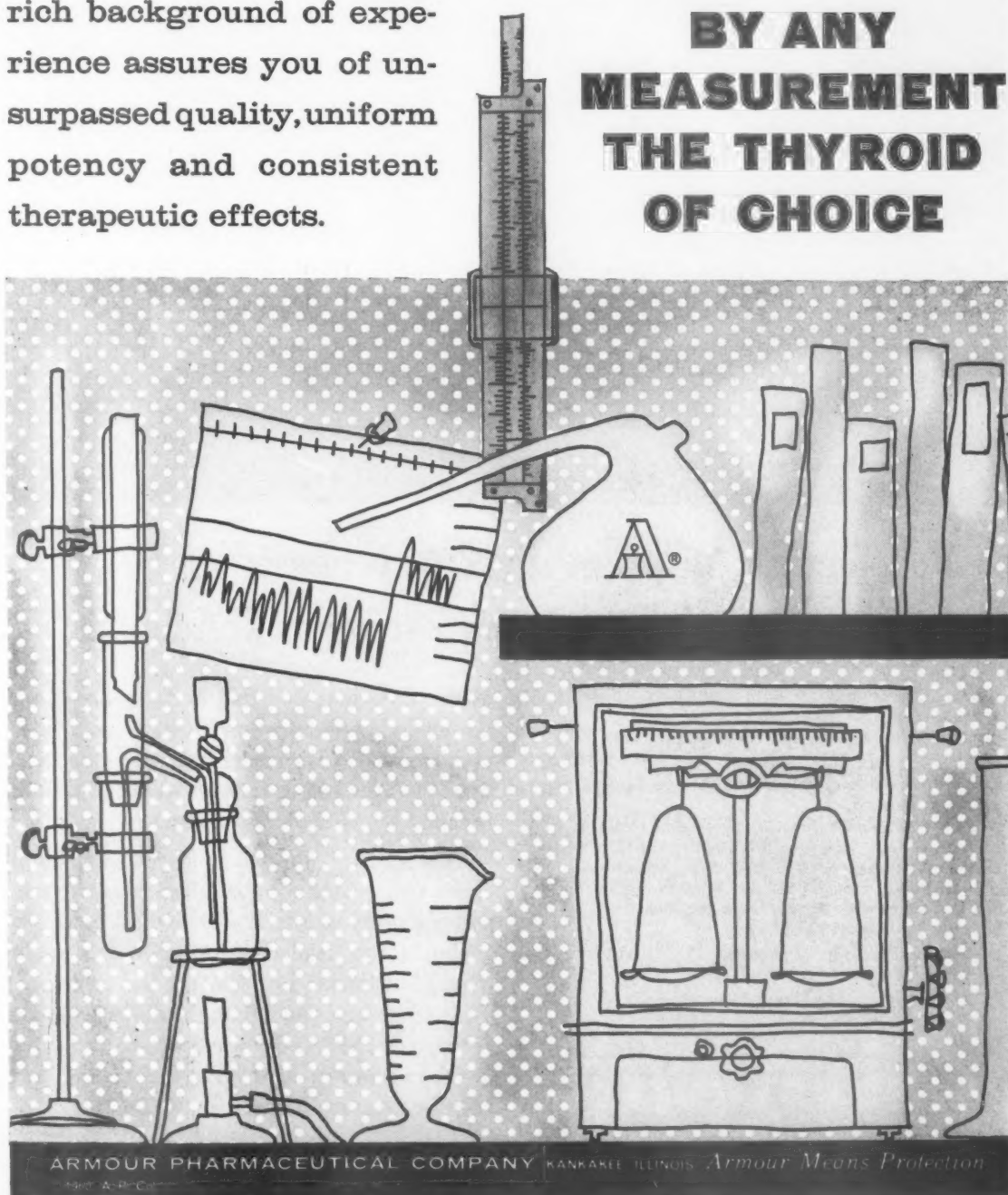
*box of 12 suppositories with applicator.*

**NITROFURANS**—a unique class of antimicrobials  
**EATON LABORATORIES, NORWICH, NEW YORK**

## ALWAYS SPECIFY ARMOUR THYROID

**ARMOUR THYROID** for over half a century has been more widely prescribed...more widely dispensed than any other thyroid product. Pioneer in thyroid standardization, Armour's rich background of experience assures you of unsurpassed quality, uniform potency and consistent therapeutic effects.

**BY ANY  
MEASUREMENT  
THE THYROID  
OF CHOICE**





**Helps you**  
**take the misery out of menopause**  
*as hormones alone often don't do*



**Fast-acting Milprem directly relieves**  
**both emotional dread and estrogen deficiency**

**Dosage:** One Milprem tablet t.i.d. in 21-day courses with one-week rest periods; during the rest periods, Miltown alone can sustain the patient.

**Composition:** Miltown (meprobamate) + conjugated estrogens (equine).

**Supplied:** **Milprem-400**, each coated pink tablet contains 400 mg. Miltown and 0.4 mg. conjugated estrogens (equine). **Milprem-200**, each coated old-rose tablet contains 200 mg. Miltown and 0.4 mg. conjugated estrogens (equine). Both potencies in bottles of 60.

*Literature and samples on request.*

**Milprem<sup>®</sup>**

(Miltown<sup>®</sup> plus natural estrogens)

CHP-1206

Many physicians find that estrogen therapy is not enough for the woman who is also filled with anxiety by her menopause. Her emotional dread may make her so miserable that it becomes a real clinical problem.

This is where Milprem helps you so much. It calms the woman's anxiety and tension; prevents moody ups and downs; relieves her insomnia and headache. At the same time, it checks hot flushes by replacing lost estrogens. The patient feels better than she did on estrogen therapy alone. And your counsel and your assurances can now help her make her adjustment much faster.



WALLACE LABORATORIES / New Brunswick, N. J.



*in inflammatory anorectal disorders...*

# Wyanooids HC<sup>®</sup>

Rectal Suppositories with Hydrocortisone, WYETH

*for symptomatic relief of*  
pruritus ani • proctitis • postoperative  
inflammatory reactions • chronic ulcerative  
colitis • irradiation proctitis

## SUPPLIED

Suppositories, boxes of 12. Each suppository contains 10 mg. hydrocortisone acetate, 15 mg. extract belladonna (0.19 mg. equiv. total alkaloids), 3 mg. ephedrine sulfate, zinc oxide, boric acid, bismuth oxyiodide, bismuth subcarbonate, and balsam peru in an oleaginous base.

Wyeth Laboratories



Philadelphia 1, Pa.

A Century of Service to Medicine

## Nonsurgical treatment of Endometriosis with

# ENOVID<sup>®</sup>

Seventeen patients<sup>1</sup> with presumed endometriosis selected for pseudopregnancy treatment were given Enovid on a "schedule of 10 mg. daily for ten days, 20 mg. daily for two weeks, and 30 mg. daily thereafter." Treatment was continued for fourteen to twenty weeks.

"They all experienced diminution or elimination of pain during treatment. Nine were entirely free of pain. Others were definitely improved but had occasional episodes of pelvic discomfort. . . . The improvement observed during treatment has generally persisted [during an average follow-up period of five months]. . . . Patients with the most extensive tenderness, nodularity, and symptoms had the best results."

The effect of Enovid in another study is described<sup>2</sup> as follows:

"Enovid is a potent, orally effective progestin. The addition of 3-methyl ether of ethynylestradiol prevents 'breakthrough' bleeding and produces an ideal mimic of the hormonal changes of pregnancy. Enovid inhibits ovulation, induces a secretory endometrium and produces a decidual effect in areas of endometriosis. It is postulated that, after five to six months of such treatment, decidual necrosis occurs and is followed by gradual absorption."

The author<sup>2</sup> recommends that this therapy be continued for a minimum of five to six months if the pseudopregnancy is being effected to avoid operation. The side effect of nausea, which usually disappears within four or five days, may be diminished by starting with 5 mg. instead of 10 mg. of Enovid, by use of an antiemetic or by administering the drug with the evening meal or with milk or an antacid.

**How Supplied:** Enovid (brand of norethynodrel with ethynylestradiol 3-methyl ether) is supplied as uncoated, scored, coral-colored tablets of 10 mg. each.

**G. D. SEARLE & CO.**

CHICAGO 80, ILLINOIS

*Research in the Service of Medicine*



1. Andrews, M. C.; Andrews, W. C., and Strauss, A. F.: Effects of Progestin-Induced Pseudopregnancy on Endometriosis: Clinical and Microscopic Studies, *Am. J. Obst. & Gynec.* 78:776 (Oct.) 1959.

2. Kistner, R. W.: Endometriosis and Infertility, *Clin. Obst. & Gynec.* 2:877 (Sept.) 1959.

# "SUNNY SIDE UP"



Specific effectiveness  
in morning sickness  
with

## MORNIDINE®

*for*

- Prevention of nausea and vomiting
- Selective action on the emetic center
- "Excellent" or "good" relief
- Little or no drowsiness

Mornidine (brand of pipamazine), another achievement of Searle Research, provides selective action on the vomiting center with very little drowsiness. Mornidine is extremely effective in morning sickness. In 145 pregnant patients, 91 per cent had "excellent" or "good" relief from nausea and vomiting.

Doses of 5 mg. at intervals of six to eight hours provide effective relief all day. Suggestion: first tablet to be taken upon awakening.

For patients unable to retain oral medication when first seen, Mornidine may be administered intramuscularly in doses of 5 mg. (1 cc.).

G. D. Searle & Co., Chicago 80, Illinois. Research in the Service of Medicine.

*faster recovery, greater comfort  
for your OB-GYN patients*



Administered before and after cervicovaginal surgery, irradiation, delivery, and office procedures such as cauterization, FURACIN CREAM promptly controls infection; reduces discharge, irritation and malodor; hastens healing. FURACIN CREAM is active in the presence of exudates, yet is nontoxic to regenerating tissue, does not induce significant bacterial resistance nor encourage monilial overgrowth.

## **FURACIN<sup>®</sup> CREAM**

BRAND OF NITROFURAZONE

FURACIN 0.2% in a fine cream base, water-miscible and self-emulsifying in body fluids. Tubes of 3 oz., with plastic plunger-type vaginal applicator. Also available: FURACIN Vaginal Suppositories.



THE NITROFURANS—a *unique* class of antimicrobials  
EATON LABORATORIES, NORWICH, NEW YORK




NOW—for more comprehensive control of

*'pain  
&  
spasm'*



- pain due to or associated with
- spasm of skeletal muscle

a NEW  muscle relaxant-analgesic

# Robaxisal<sup>®</sup>

ROBAXIN<sup>®</sup> WITH ASPIRIN

ROBAXISAL, a new dual-acting muscle relaxant-analgesic, effectively treats both skeletal muscle spasm and severe pain due to or associated with the spasm. Each Tablet contains:

- A relaxant component—Robaxin\*—widely recognized for its prompt, long-lasting relief of painful skeletal muscle spasm, with unusual freedom from undesired side effects. . . . . 400 mg.  
\*Methocarbamol 'Robins' U.S. Pat. No. 2770649.
- An analgesic component—aspirin—whose pain-relieving effect is markedly enhanced by Robaxin, and which has added value as an anti-inflammatory and anti-rheumatic agent. . . (5 gr.) 325 mg.

INDICATIONS: ROBAXISAL is indicated when analgesic as well as relaxant action is desired in the treatment of skeletal muscle spasm and severe concurrent pain. Typical conditions are disorders of the back, whiplash and other traumatic injuries, myositis, and pain and spasm associated with arthritis.

SUPPLY: ROBAXISAL Tablets (pink-and-white, laminated) in bottles of 100 and 500.

Also available: ROBAXIN Injectable, 1.0 Gm. in 10-cc ampul. ROBAXIN Tablets, 0.5 Gm. (white, scored) in bottles of 50 and 500.

**A. H. ROBINS CO., INC., Richmond 20, Va.**

*Making today's medicines with integrity  
... seeking tomorrow's with persistence*

# YUM

(translation: a little real salt can mean a lot in edema and hypertension)



Think of mashed potatoes without the pinch of salt. Unthinkable? Not for the edema or heart patient, who may live with such dreary fare day after day. A good diuretic like Oretic offers a chance of welcome relief from this tasteless pattern. Potent enough to treat the more serious aspects of edema, and valuable in management of mild to moderate hypertension, Oretic produces a marked elimination of water and sodium. And the saluretic effect paves the way for your exploration of revised meal plans and somewhat relaxed dietary restrictions. Oretic offers no 100% relief for low-sodium diets, of course. But adjustment should be possible in enough cases to make it worth considering on an individual basis. The individual lucky enough to get a little of the real pleasure of real salt back on the table will surely thank you.

**ORETIC®**  
(Hydrochlorothiazide, Abbott)



a potent means when the end is  
saluresis. Tablets, 25- and 50-mg.



007252



A satisfactory hematologic picture during the second year of life may often be assured before the second year begins. Timely prophylaxis—Similac With Iron feeding during the first year of life—can help assure adequate iron stores; can help prevent dilution of hemoglobin in an expanding blood compartment. When exogenous iron is prescribed for the infants in your practice, Similac With Iron—from the bottle or from a cup—provides assured iron intake in every formula feeding.

## **SIMILAC WITH IRON®**

12 mg of ferrous iron per quart of formula



**ROSS LABORATORIES**  
Columbus 16, Ohio



Just one prescription  
for new  
**ORETICYL<sup>TM</sup>**

(Oretic® with Harmony!®)

**keeps your hypertensives  
wide awake & working**







#### GIVE THEM THE BENEFITS OF

- 1 ORETIC's pronounced saluresis
- 2 HARMONYL's selective antihypertensive effect
- 3 Potentiating action of both agents working together

When Harmony, Abbott's unique rauwolfia alkaloid, is combined with the potent diuretic/antihypertensive Oretic, the result is convenient, efficient one-tablet treatment especially suited to hypertensives who must stay alert and active during the day.

Oretic keeps hypertensives wide awake and working because Harmony has a selective action. It lowers blood pressure without undue side effects. For example, in a series of studies<sup>1,2,3</sup> of 403 hypertensive and mixed anxiety patients treated with Harmony alone, only 6 reported any depression; only 12 reported any nasal stuffiness; only 13 reported any lethargy.

Oretic potentiates the antihypertensive action of Harmony, and also produces elimination of water and sodium. Thus, in many cases some relaxation of rigid low-salt diets may be allowed.

To further tailor therapy to the needs of the individual patient, three precision dose forms are available:

**Oretic Forte.** Oretic 25 mg.,  
Harmony, 0.25 mg.

**Oretic 25.** Oretic 25 mg.,  
Harmony, 0.125 mg.

**Oretic 50.** Oretic 50 mg.,  
Harmony, 0.125 mg.

All in bottles of 100 and 1000.

1. Billow, B. W. et al., The Use of a New Rauwolfia Derivative, Deserpidine, in Mild Functional Disturbances and Office Psychiatry, N. Y. J. Med., 59:1769, May, 1959.

2. Winsor, T., Comparative Effects of Various Rauwolfia Alkaloids in Hypertension, Diseases of the Chest, April, 1959.

3. Rawls, W. B. and Evans, W. L., Jr., Clinical Experiences with Deserpidine in the Management of Hypertension and Anxiety Neurosis, N. Y. J. Med., 59:1774, May, 1959.

ORETIC—TRADEMARK FOR ORETIC WITH HARMONYL  
ORETIC—HYDROCHLOROTHIAZIDE, ABBOTT  
HARMONYL—DESERPIDINE, ABBOTT



## MORE THAN MEETS THE EYE...



Physicians know that in every pint of blood lie vital hidden treasures.

The AMERICAN RED CROSS knows this, too. Through the Blood Program, licensed by the National Institutes of Health, it provides

- whole blood to hospitals served by the program
- blood for national emergencies
- blood derivatives to physicians and hospitals . . . serum albumin, gamma globulin, fibrinogen, fresh-frozen plasma and packed red cells
- crude fractions for research

Encourage donors to expand the availability of life's most precious fluid by giving blood wherever there are facilities for receiving it.

# FOSFREE

## To Simplify & Assist PRENATAL MANAGEMENT

Fosfree Tablets aid in the management, prevention, and control of these "Problems of Pregnancy"

- NAUSEA
- ANEMIA
- LEG CRAMPS
- VITAMIN AND MINERAL DEFICIENCY

*Soluble Phosphorous Free Calcium, High Pyridoxine, Vitamin B-12, Ferrous Gluconate plus Catalyst.*

*Recommended Dosage: 4 Tablets per day  
Samples Upon Request*

# Mission

Quality through Control

PHARMACAL CO.

SAN ANTONIO 6, TEXAS



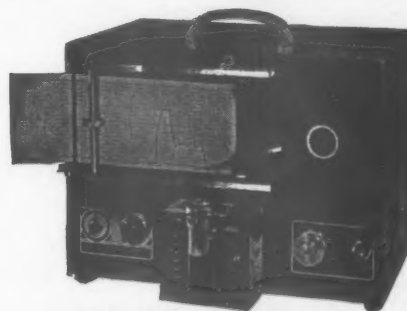
*26 25 Years  
Successful Use  
Without a Diaphragm*

**SINCE 1934**

WHITTAKER LABORATORIES, Inc.  
PEEKSKILL, NEW YORK.

## HAILED BY DOCTORS EVERYWHERE

FOR SIMPLICITY, ACCURACY & SAFETY



### GRAFAX MODEL "S"

KYMOINSUFFLATOR

FOR TUBAL INSUFFLATION

- Permanent records—400 tests per roll
- Standard cylinder contains CO<sub>2</sub> for 500 tests
- Controlled adjustable maximum pressure
- Lowest in cost—to buy, operate and maintain
- Compact & portable—weighs only 15 lbs.

Send for descriptive literature

GRAFAX INSTRUMENT CO., Dept. G  
517 West 45th Street  
New York 36, N. Y.

**F***irst emphasis is on*  
PAIN RELIEF  
*in sprains, strains, arthritis, rheumatism*

*not only relieves pain but also relaxes taut muscles*

**SAFE POTENT FAST**

**SOMA**<sup>T.M.</sup>

*(carisoprodol Wallace)*

Samples and literature on request

 **WALLACE LABORATORIES, Cranbury, New Jersey**



# INDEX TO ADVERTISERS

<b>Agoral</b> Warner-Chilcott ----- 33	<b>Formaldehyde Germicide</b> Bard-Parker Company, Inc. -- 92	<b>Oretic</b> Abbott Laboratories ----- 122
<b>Americaine</b> Arnar-Stone Laboratories, Inc. 22	<b>Fosfree</b> Mission Pharmacal Co. ----- 127	<b>Oreticyl</b> Abbott Laboratories ---- 124, 125
<b>Amsco Surgical Chair</b> American Sterilizer ----- 16	<b>Furacin Cream</b> Eaton Laboratories ----- 120	<b>Pet Instant Nonfat Dry Milk</b> Pet Milk Company ----- 97
<b>Appetrol</b> Wallace Laboratories ----- 112	<b>Furacin-HC Cream</b> Eaton Laboratories ----- 54	<b>Phenergan</b> Wyeth Laboratories ----- 63
<b>Armour Thyroid</b> Armour Pharmaceutical Com- pany ----- 115	<b>Furadantin</b> Eaton Laboratories ----- 32, 101	<b>Pitocin</b> Parke, Davis & Company --- 81
<b>Atarax</b> J. B. Roerig & Company --- 111	<b>Gelusil</b> Warner-Chilcott ----- 49	<b>PMB 200</b> Ayerst Laboratories ----- 26
<b>Bonadoxin</b> J. B. Roerig & Company ---- 73	<b>Gentia-Jel</b> Westwood Pharmaceuticals -- 37, 38	<b>Powder</b> The S. E. Massengill Co. -- 55, 56
<b>Bonine</b> Pfizer Laboratories ----- 51	<b>Grafax Model "S"</b> Grafax Instrument Co. ----- 127	<b>Pramilets</b> Abbott Laboratories ----- 20, 21
<b>Carnation Instant Nonfat Dry Milk</b> Carnation Company ----- 107	<b>Hist-A-Corte</b> Dome Chemicals Inc. ----- 85	<b>Precalcins</b> Walker Laboratories, Inc. ---- 130
<b>Caroid &amp; Bile Salts</b> American Ferment Co., Inc. 86	<b>Hydro-Diuril</b> Merck Sharp & Dohme --- 58, 59	<b>Premarin</b> Ayerst Laboratories ----- 96
<b>Chymar</b> Armour Pharmaceutical Com- pany ----- 61	<b>Hygroton</b> Geigy Pharmaceuticals ----- 47	<b>Proloid</b> Warner-Chilcott ----- 7
<b>Citrus Bioflavonoids</b> Sunkist Growers ----- 76, 77	<b>Koromex</b> Holland-Rantos Co., Inc. ---- 99	<b>Ramses</b> Julius Schmid, Inc. ----- 60
<b>Combidi</b> Smith Kline & French Labora- tories ----- 95	<b>Lanesta Gel</b> George A. Breon & Co. ---- 13	<b>Rauwiloid</b> Riker Laboratories -- Third Cover
<b>Compazine</b> Smith Kline & French Labora- tories ----- 42	<b>Leritine</b> Merck Sharp & Dohme ----- Fourth Cover	<b>Ritalin</b> Ciba Pharmaceutical Products 24, 25
<b>Cooper Creme</b> Whittaker Laboratories, Inc. 127	<b>Librium</b> Roche Laboratories -- Second Cover	<b>Robaxin</b> A. H. Robins Co., Inc. ---- 36
<b>Cytran</b> The Upjohn Company ---- 70, 71	<b>Livitamin</b> The S. E. Massengill Co. -- 17, 18	<b>Robaxial</b> A. H. Robins Co., Inc. ---- 121
<b>Delfen</b> Ortho Pharmaceutical Corpora- tion ----- 45	<b>Lubafax</b> Burrroughs Wellcome & Co. (U.S.A.) Inc. ----- 46	<b>Roncovite-MF</b> Lloyd Brothers, Inc. ----- 52
<b>Deprol</b> Wallace Laboratories ----- 109	<b>Mepergan</b> Wyeth Laboratories ----- 103	<b>Senokot</b> The Purdue Frederick Company 9
<b>Desitin Suppositories</b> Desitin Chemical Company -- 23	<b>Mephyton</b> Merck Sharp & Dohme ----- 29	<b>Similac</b> Ross Laboratories ----- 123
<b>Desplex</b> Amfre-Grant, Inc. ----- 43	<b>Meprospan-400</b> Wallace Laboratories ----- 48	<b>S-M-A</b> Wyeth Laboratories ----- 30, 31
<b>Dienestrol</b> Ortho Pharmaceutical Corpora- tion ----- 93	<b>Metamucil</b> G. D. Searle & Co. ----- 75	<b>Soma</b> Wallace Laboratories ----- 128
<b>Dorbane</b> SchenLabs Pharmaceuticals, Inc. 50	<b>Metrecal</b> Mead Johnson & Co. ---- 40, 41	<b>Stelazine</b> Smith Kline & French Labora- tories ----- 3
<b>Doxidan</b> Lloyd Brothers, Inc. ----- 44	<b>Milibis</b> Winthrop Laboratories ----- 69	<b>Tampax</b> Tampax Incorporated ----- 87
<b>Dulcolax Suppositories</b> Geigy Pharmaceuticals ----- 39	<b>Milprem</b> Wallace Laboratories ----- 116	<b>Tigan</b> Roche Laboratories ----- 64, 65
<b>Dyclone</b> Pitman-Moore Company ----- 94	<b>Miltown</b> Wallace Laboratories ----- 14, 15	<b>Triburon</b> Roche Laboratories ----- 34, 35
<b>Edrisal</b> Smith Kline & French Labora- tories ----- 84	<b>Mol-Iron</b> White Laboratories, Inc. ---- 5	<b>Tricofuron</b> Eaton Laboratories ----- 114
<b>En-Cebrin</b> Eli Lilly and Company ----- 74	<b>Mornidine</b> G. D. Searle & Co. ----- 119	<b>Triple Sulta Cream</b> Ortho Pharmaceutical Corpora- tion ----- 19
<b>Enfamil</b> Mead Johnson & Company -- 72	<b>Natalins Comprehensive</b> Mead Johnson & Co. ----- 68	<b>Tucks</b> Fuller Pharmaceutical Co. -- 89
<b>Enovid</b> G. D. Searle & Co. ----- 118	<b>Niamid</b> Pfizer Laboratories ----- 62	<b>Urised</b> Chicago Pharmacal Company 27
<b>Equanil</b> Wyeth Laboratories ----- 79	<b>"Nine Months of Reading"</b> Doubleday & Company, Inc. 11	<b>Vagisec</b> Julius Schmid, Inc. ----- 57
<b>Estrosed</b> Chicago Pharmacal Company -- 28	<b>Norlutin</b> Parke, Davis & Company ---- 91	<b>Vasodilan</b> Mead Johnson & Company -- 113
<b>ET-3</b> Biochemical Procedures ----- 90	<b>Nugestoral</b> Organon Inc. ----- 53	<b>Vi-Drape Film</b> Aeroplast Corporation -- 104, 105
<b>Ethiodol</b> E. Fougera & Company, Inc. 78	<b>Nupercainal</b> Ciba Pharmaceutical Products 82	<b>White Cotton Gowns</b> Teckla ----- 110
<b>Filibon</b> Lederle Laboratories ----- 98	<b>Nylmerate</b> Holland-Rantos Co., Inc. ---- 83	<b>Wyanoids HC</b> Wyeth Laboratories ----- 117
<b>Fleet Enema</b> C. B. Fleet Co., Inc. ----- 88	<b>Obstetrical &amp; Gynecological In- struments</b> J. Sklar Manufacturing Co. 102	<b>Zactirin</b> Wyeth Laboratories ----- 100

While every precaution is taken to insure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.

**gas is for balloons...  
not for  
pregnant  
women**



Unlike most prenatal supplements, the PRECALCINS do *not* generate carbon dioxide gas when ingested (see above). Thus, patients experience more comfortable pregnancies—*without* therapy-induced belching, gas pains, or gastric distention. What's more, the PRECALCINS supply more vitamins, minerals, and bioflavonoids than most other one-a-day supplements... and at a low, low cost per day. So give your patients *gas-free* supplementation and make every pregnancy as nutritionally perfect as it is comfortable.

**prescribe the *Precalcins*  
for gas-free prenatal nutritional support**

**PRECALCIN®:** A complete one-capsule-daily vitamin and mineral formula containing calcium and phosphorus (as dicalcium phosphate); bottles of 100, 500 and 1,000. **PRECALCIN® LACTATE:** A complete one-capsule-daily vitamin and mineral formula containing calcium (as lactate) *without* phosphorus; bottles of 100, 500 and 1,000. **PRECALCIN®-D:** A one-dose-daily, two-capsule formulation providing *extra-generous* amounts of calcium (as lactate and phosphate, 1200 mg.); bottles of 60 and 300 pink and blue capsules — the pink capsules containing vitamins and minerals, the blue capsules containing calcium.

**WALKER LABORATORIES, INC., MOUNT VERNON, NEW YORK**

THE RECOMMENDED DAILY DOSES PRODUCE THIS MUCH GAS — BUT NOT THE PRECALCINS—These balloons dramatically demonstrate the amount of carbon dioxide gas released when the recommended daily doses of six of today's most frequently prescribed prenatal supplements are dropped into simulated gastric juice. The outstanding exception seen here is PRECALCIN which, like PRECALCIN LACTATE and PRECALCIN-D, produces no gas. The reason is simple: All three PRECALCINS contain well-tolerated, *gas-free* sources of calcium — as lactate and/or phosphate — while the other five supplements contain calcium carbonate. When the carbonate salt reacts with gastric juice ( $\text{CaCO}_3 + 2\text{HCl} \rightarrow \text{CO}_2 \uparrow + \text{CaCl}_2 \downarrow + \text{H}_2\text{O}$ ), carbon dioxide is liberated—both in the test tube and in the stomach. So avoid such gaseous discomforts of pregnancy. Prescribe the PRECALCINS.

# In Hypertension

and

# Anxiety States

Just  
two  
tablets  
at bedtime

# CONTROL

with MAXIMUM SAFETY

## RAUWILOID<sup>®</sup>

alseroxylon 2 mg.

### In Hypertension

Simplicity of control based on negligible incidence of serious side actions, simplicity of dosage, and applicability to a wide range of patients.

### In Anxiety States

Rauwiloid is outstanding for its calming, non-soporific sedation in anxiety states...without hypertension.

**Compatible** with other anti-hypertensive medications. Potentiates therapeutic action of more potent agents and permits their use in reduced and better tolerated dosage.

When more potent hypotensive action is needed, prescribe one of these convenient single-tablet combinations

**Rauwiloid<sup>®</sup> + Veriloid<sup>®</sup>**  
alseroxylon 1 mg. and alkavervir 3 mg.

or

**Rauwiloid<sup>®</sup> + Hexamethonium**  
alseroxylon 1 mg. and hexamethonium  
chloride dihydrate 250 mg.

Patients with severe hypertension often can be maintained on Rauwiloid alone after desired blood pressure levels are reached with combination medication.



Northridge, California



MAR - 6 1964

# ANOTHER STUDY<sup>1</sup> CONFIRMS: EXCELLENT OBSTETRIC ANALGESIA WITH LERITINE

Clinical results with LERITINE in 155 obstetric patients.

■ **rapid relief of pain:** "onset of action is rapid," with "almost immediate analgesia and sedation" and "an analgesic potency 2½ times that of meperidine . . ."

■ **wide margin of safety:** "respiratory depression or alteration in blood pressure was not observed . . . nausea and vomiting during labor were extremely rare . . ."

■ **minimal effect on newborns:** "condition of the infant at the time of delivery . . . when compared with a group sedated with meperidine . . . shows a consistently higher rating."

■ **high patient acceptance:** "We were able to obtain good to excellent amnesia in 64-66% of mothers and subjective satisfaction with the method in 83-85% of cases."

1. Wizenberg, M. J., et al.: Am. J. Obst. & Gynec. 78: 405 (Aug.) 1959.

**Leritine**<sup>\*</sup>  
(anileridine)

effective even for  
**intense pain**

parenterally or orally



Additional literature on LERITINE is available to physicians on request.

WARNING: LERITINE may be habit-forming. Subject to Federal Narcotic Law.

\*LERITINE is a trademark of Merck & Co., Inc.



**Merck Sharp & Dohme**, DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.